Gomella Lauds Breakthroughs in GU Cancers

Leonard G. Gomella, MD, FACS
INDICATIONS
Retevmo is a kinase inhibitor indicated for the treatment of:

- adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)
- 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 (ORR) and duration of response (DoR). Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION
Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years). Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retevmo based on the severity.

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertensive medications. Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. 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 Retevmo based on the severity.

Please see Important Safety Information and Brief Summary of Prescribing Information for Retevmo on subsequent pages.
Response in patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC), advanced or metastatic RET fusion-positive thyroid cancer (non-medullary thyroid cancer (non-MTC)), and advanced or metastatic RET-mutant MTC.

### Treatment-naive (n=39)

- **85% ORR**
  - (95% CI: 70, 94)
  - 0% CR + 85% PR
  - Median DoR
    - not yet reached (95% CI: 12, NE; median follow-up: 7.4 months)

### Previously treated with platinum chemotherapy (n=105)

- **64% ORR**
  - (95% CI: 54, 73)
  - 1.9% CR + 62% PR
  - Median DoR
    - was 17.5 months (95% CI: 12, NE; median follow-up: 12.1 months)

### Responses in intracranial lesions were observed in 10 of 11 previously treated patients with measurable brain metastases

- No patients received radiation therapy to the brain within 2 months prior to study entry

### Advanced or Metastatic RET Fusion-Positive Thyroid Cancer (Non-MTC)

- **100% ORR**
  - (95% CI: 63, 100)
  - 12.5% CR + 88% PR
  - Median DoR
    - not yet reached (95% CI: NE; median follow-up: 8.8 months)

### Advanced or Metastatic RET-Mutant MTC

- **79% ORR**
  - (95% CI: 54, 94)
  - 5.3% CR + 74% PR
  - Median DoR
    - was 18.4 months (95% CI: 7.6, NE; median follow-up: 17.5 months)

- **73% ORR**
  - (95% CI: 62, 82)
  - 11% CR + 61% PR
  - Median DoR
    - was 22.0 months (95% CI: NE; median follow-up: 7.8 months)

- **69% ORR**
  - (95% CI: 55, 81)
  - 9% CR + 60% PR
  - Median DoR
    - not yet reached (95% CI: 19.1, NE; median follow-up: 14.1 months)

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### Adverse Reactions and Laboratory Abnormalities

- The most common adverse reactions, including laboratory abnormalities, (≥25%) were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation.

- Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequent serious adverse reaction in ≥2% of patients was pneumonia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in ≥1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3). Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received Retevmo. Adverse reactions resulting in permanent discontinuation in patients who received Retevmo included increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).

- Dose interruptions due to an adverse reaction occurred in 42% of patients who received Retevmo. Adverse reactions requiring dosage interruption in ≥2% of patients included ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation.

- Dose reductions due to an adverse reaction occurred in 31% of patients who received Retevmo. Adverse reactions requiring dosage reductions in ≥2% of patients included ALT increased, AST increased, QT prolongation, and fatigue.

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Retevmo can cause concentration-dependent QT interval prolongation. An increase in QTcF interval >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. Retevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradycardia, arrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

Serious, including fatal, hemorrhagic events can occur with Retevmo. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with Retevmo including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

Hypersensitivity occurred in 4.3% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminists. If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, Retevmo has the potential to adversely affect wound healing. Withhold Retevmo for at least 7 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 Retevmo after resolution of wound healing complications has not been established.

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose. There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on 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 Retevmo and for 1 week after the final dose.

Serious adverse reactions (Grade 3–4) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were hypertension (18%), prolonged QT interval (4%), diarrhea (3.4%), dyspnea (2.3%), fatigue (2%), abdominal pain (1.5%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequently reported serious adverse reaction (in ≥ 2% of patients) was pneumonia.

Please see Brief Summary of Prescribing Information for Retevmo on subsequent pages.

**INDICATIONS AND USAGE**

RETEVMO (selpercatinib) is a kinase inhibitor indicated for the treatment of:

- Adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutated 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 are radioactive iodine-refractory (if radioactive iodine is appropriate)

**CONTRAINDICATIONS:** None

**WARNINGS AND PRECAUTIONS**

- Hypertoxicitiy
- Serious hepatic adverse reactions occurred in 2.6% of patients treated with RETEVMO. Increased AST occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased ALT occurred in 45% of patients, including Grade 3 or 4 events in 8%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years).
- Monitor ALT and AST prior to initiating RETEVMO, every two weeks for the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue RETEVMO based on the severity.

**Hypertension**

- Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.4% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertensive medications.
- Do not initiate RETEVMO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating RETEVMO. 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 RETEVMO based on the severity.

**QT Interval Prolongation**

- RETEVMO can cause concentration-dependent QT interval prolongation. An increase in QTcF interval to >550 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. RETEVMO has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction.
- Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradycardia/tachycardia, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment. Adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hyperkalemia and hypocalcemia prior to initiating RETEVMO and during treatment.
- Monitor the QT interval more frequently when RETEVMO is concomitantly administered with strong and moderate CYP3A4 inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue RETEVMO based on the severity.

**Hemorrhagic Events**

- Serious including fatal hemorrhagic events can occur with RETEVMO. Grade ≥ 3 hemorrhagic events occurred in 2.3% of patients treated with RETEVMO including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis.
- Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage.

**Hypersensitivity**

- Hypersensitivity occurred in 4.3% of patients receiving RETEVMO, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range: 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminas.
- If hypersensitivity occurs, withhold RETEVMO and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume RETEVMO at a reduced dose and increase the dose of RETEVMO by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue RETEVMO for recurrent hypersensitivity.

**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.

**Serious Adverse Reactions**

- Serious adverse reactions occurred in 33% of patients who received RETEVMO. The most frequent serious adverse reaction (in ≥ 2% of patients) was pneumonia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in ≥ 1 patient included sepsis (n = 3), cardiac arrest (n = 3) and respiratory failure (n = 3).
- Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received RETEVMO. Adverse reactions occurring in permanent discontinuation included increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).
- Dosage interruptions due to an adverse reaction occurred in 42% of patients who received RETEVMO. Adverse reactions requiring dosage interruption in ≥ 2% of patients included ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation.
- Dose reductions due to an adverse reaction occurred in 31% of patients who received RETEVMO. Adverse reactions requiring dosage reductions in ≥ 2% of patients included ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation. The most common adverse reactions, including laboratory abnormalities, ≥ 25% were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation.

**Table 1:** Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4 (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypersensitivity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[No data provided]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pregnancy**

- RETEVMO can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant women may cause fetal harm. Those observed at the recommended human dose of 160 mg twice daily resulted in embryopathy and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for at least 1 week after the final 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.

**RET Gene Fusion or Gene Mutation Positive Solid Tumors**

- The pooled safety population described in the WARNINGS and PRECAUTIONS and below reflects exposure to RETEVMO as a single agent at 160 mg orally twice daily evaluated in 702 patients in LIBRETTO-001. Among 702 patients who received RETEVMO, 65% were exposed for 6 months or longer and 34% were exposed for greater than one year. Among these patients, 93% received at least one dose of RETEVMO at the recommended dosage of 160 mg orally twice daily.
- The median age was 59 years (range: 15 to 92 years): 0.3% were pediatric patients 12 to 16 years of age; 52% were male; and 69% were White; 22% were Asian; 5% were Hispanic/Latino, and 3% were Black. The most common tumors were NSCLC (41%), MTC (44%), and non-metastatic thyroid carcinoma (6%).

**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.

**Serious Adverse Reactions**

- Serious adverse reactions occurred in 33% of patients who received RETEVMO. The most frequent serious adverse reaction (in ≥ 2% of patients) was pneumonia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in ≥ 1 patient included sepsis (n = 3), cardiac arrest (n = 3) and respiratory failure (n = 3).
- Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received RETEVMO. Adverse reactions occurring in permanent discontinuation included increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).
- Dosage interruptions due to an adverse reaction occurred in 42% of patients who received RETEVMO. Adverse reactions requiring dosage interruption in ≥ 2% of patients included ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation.
- Dose reductions due to an adverse reaction occurred in 31% of patients who received RETEVMO. Adverse reactions requiring dosage reductions in ≥ 2% of patients included ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation. The most common adverse reactions, including laboratory abnormalities, ≥ 25% were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation.

**Table 1:** Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4 (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37</td>
<td>3.4</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>0.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23</td>
<td>1.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>35</td>
<td>18</td>
</tr>
</tbody>
</table>
Table 2: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001 (Cont.)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RETEVMO (n=702)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>35</td>
</tr>
<tr>
<td>Edema</td>
<td>33</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>27</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>23</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16</td>
</tr>
<tr>
<td>Investigations</td>
<td>17</td>
</tr>
<tr>
<td>Blood and Lymphatic System</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>15</td>
</tr>
</tbody>
</table>

1 Diarrhea includes diarrhea, defecation urgency, frequent bowel movements, and anal incontinence.
2 Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain.
3 Fatigue includes fatigue, asthenia, malaise.
4 Edema includes edema, edema peripheral, face edema, eye edema, eyelid edema, generalized edema, localized edema, lymph edema, scrotal edema, peripheral swelling, scrotal swelling, swelling face, eye swelling, peripheral swelling.
5 Includes rash, rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash pruritic.
6 Includes headache, sinus headache, tension headache.
7 Includes cough, productive cough.
8 Includes dyspnea, dyspnea exertional, dyspnea at rest.
9 Hemorrhage includes epistaxis, hematuria, hemoptysis, contusion, rectal hemorrhage, vaginal hemorrhage, ecchymosis, hematoma, ecchymosis, hematoma.
10 Includes rash, rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash pruritic.

Clinically relevant adverse reactions in ≥15% of patients who received RETEVMO include hypothyroidism (9%).

Table 2 summarizes the laboratory abnormalities in LIBRETTO-001.

Table 2- Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-001

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RETEVMO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>51</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>44</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>42</td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>41</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>37</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>36</td>
</tr>
<tr>
<td>Increased total cholesterol</td>
<td>31</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>24</td>
</tr>
<tr>
<td>Increased potassium</td>
<td>24</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>23</td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>22</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>43</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>33</td>
</tr>
</tbody>
</table>

1 Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 675 to 692 patients.

Increased Creatinine

In healthy subjects administered RETEVMO 160 mg orally twice daily, serum creatinine increased 18% after 10 days. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

DRUG INTERACTIONS

Effects of Other Drugs on RETEVMO

Acid-Reducing Agents

Concomitant use of RETEVMO with acid-reducing agents decreases selpercatinib plasma concentrations, which may reduce RETEVMO anti-tumor activity. Avoid concomitant use of PPIs, H2 receptor antagonists, and locally acting antacids with RETEVMO. If coadministration cannot be avoided, take RETEVMO with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally acting antacid).

Strong and Moderate CYP3A Inhibitors

Concomitant use of RETEVMO with a strong or moderate CYP3A inhibitor increases selpercatinib plasma concentrations, which may increase the risk of RETEVMO adverse reactions, including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A inhibitors with RETEVMO. If concomitant use of strong or moderate CYP3A inhibitors cannot be avoided, reduce the RETEVMO dosage and monitor the QT interval with ECGs more frequently.

Strong and Moderate CYP3A Inducers

Concomitant use of RETEVMO with a strong or moderate CYP3A inducer decreases selpercatinib plasma concentrations, which may reduce RETEVMO anti-tumor activity. Avoid coadministration of strong or moderate CYP3A inducers with RETEVMO.

Effects of RETEVMO on Other Drugs

CYP2C8 and CYP3A Substrates

RETREVMO is a moderate CYP2C8 inhibitor and a weak CYP3A inhibitor. Concomitant use of RETEVMO with CYP2C8 and CYP3A substrates increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of RETEVMO with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

Drugs that Prolong QT Interval

RETREVMO is associated with QTc interval prolongation. Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings from animal studies, and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. There are no available data on RETEVMO use in pregnant women to inform drug-associated risk. Administration of selpercatinib to pregnant rats during the period of organogenesis resulted in embryolethality and malformations at maternal exposures that were approximately equal to the human exposure at the clinical dose of 160 mg twice 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% to 4% and 15% to 20%, respectively.

Data

Animal Data

Selpercatinib administration to pregnant rats during the period of organogenesis at oral doses ≥ 100 mg/kg (approximately 3.6 times the human exposure based on the area under the curve [AUC] at the clinical dose of 160 mg twice daily) resulted in 100% post-implantation loss. At the dose of 50 mg/kg (approximately equal to the human exposure [AUC] at the clinical dose of 160 mg twice daily), 6 of 8 females had 100% early resorptions; the remaining 2 females had high levels of early resorptions with only 3 viable fetuses across the 2 litters. All viable fetuses had decreased fetal body weight and malformations (2 with short tail and one with small snout and localized edema of the neck and thorax).

Lactation

Risk Summary

There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on 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 RETEVMO and for 1 week after the final dose.
### Laboratory Abnormalities (≥ 20% Worsening from Baseline in Patients Who

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Denominator</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased platelets</td>
<td>33</td>
<td>2.7</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>43</td>
<td>1.6</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>24</td>
<td>0.6</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>37</td>
<td>1.0</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>44</td>
<td>2.2</td>
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<tr>
<td>Increased ALT</td>
<td>45</td>
<td>9</td>
</tr>
<tr>
<td>Increased AST</td>
<td>51</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35</td>
<td>2*</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Cough</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Rash</td>
<td>5</td>
<td>27</td>
</tr>
</tbody>
</table>

**Investigations**
- Hemorrhage: hemorrhage, melena, mouth hemorrhage, occult blood positive, pelvic hematoma, periorbital bleeding, hematemesis, hemorrhagic anemia, intraabdominal hemorrhage, lower gastrointestinal diverticulum intestinal hemorrhagic, eye hemorrhage, gastrointestinal hemorrhage, gingival intracranial, spontaneous hematoma, abdominal wall hematoma, angina bullosa hemorrhagica, blood blister, blood urine present, cerebral hemorrhage, gastric hemorrhage, hemorrhage
- Dyspnea: dyspnea, respiratory distress, respiratory rate greater than 30 breaths/minute, respiratory discomfort, gastrointestinal pain
- Anal incontinence

### Risk Summary

**Pregnancy**
- Based on animal data, RETEVMO can cause embryolethality and malformations at doses resulting in exposures less than or equal to the human exposure at the clinical dose of 160 mg twice daily.

**Contraception**
- Advise female patients of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the final dose.

**Infertility**
- RETEVMO may impair fertility in females and males of reproductive potential.

**Pediatric Use**
- The safety and effectiveness of RETEVMO have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced RET fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of RETEVMO for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. The safety and effectiveness of RETEVMO have not been established in these indications in patients less than 12 years of age.

**The safety and effectiveness of RETEVMO have not been established in pediatric patients for other indications.**

**Animal Toxicity Data**
- In 4-week general toxicology studies in rats, animals showed signs of physeal hypertrophy and tooth dysplasia at doses resulting in exposures < approximately 3 times the human exposure at the 160 mg twice daily clinical dose. Minipigs also showed signs of minimal to marked increases in physeal thickness at the 15 mg/kg high dose level (approximately 0.3 times the human exposure at the 160 mg twice daily clinical dose). Rats in both the 4- and 13-week toxicology studies had malocclusion and tooth discoloration at the high dose levels (>1.5 times the human exposure at the 160 mg twice daily clinical dose) that persisted during the recovery period.

**Geriatric Use**
- Of 702 patients who received RETEVMO, 34% (239 patients) were ≥ 65 years of age and 10% (67 patients) were ≥ 75 years of age. No overall differences were observed in the safety or effectiveness of RETEVMO between patients who were ≥65 years of age and younger patients.

**Renal Impairment**
- No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance [CrCl] >30 mL/min, estimated by Cockcroft-Gault). The recommended dosage has not been established for patients with severe renal impairment (CrCl <30 mL/min) or end-stage renal disease.

**Hepatic Impairment**
- Reduce the dose when administering RETEVMO to patients with severe (total bilirubin greater than 3 to 10 times upper limit of normal [ULN] and any AST) hepatic impairment. No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) or moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST) hepatic impairment. Monitor for RETEVMO-related adverse reactions in patients with hepatic impairment.

**Rx only.**

Additional information can be found at www.retevmo.com.

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SE HCP BS 06MAY2020

RETEVMO™ (selpercatinib) capsules, for oral use.

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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 64.
Visit OncLive.com for more information or use your smartphone to scan this QR code

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www.OncLive.com

Gomella Lauds Breakthroughs in GU Cancers

by LARRY HANOVER

New drug approvals and advances in imaging for patients with prostate cancer are among the developments fueling excitement in urologic cancer care that will be featured during the New York GU™ 14th Annual Interdisciplinary Prostate Cancer Congress® and Other Genitourinary Malignancies meeting in March. Leonard G. Gomella, MD, FACS, one of the conference cochairs, discusses the implications of key advances with OncologyLive®.

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It’s Time to Rethink 4 Unique Cancer Terms
By Maurie Markman, MD

From the Physician

Should All Elderly Patients With Newly Diagnosed Multiple Myeloma Receive Monoclonal Antibodies?
By Marc Braunstein, MD, PhD

COVID-19 in the Clinic

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NCCN Releases COVID-19 Vaccination Guidance for Patients With Cancer

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60 Practices Grapple With an Aging Oncology Workforce
By Deborah Abrams Kaplan
There’s Good News in Prostate Cancer Care

DEVELOPMENTS IN PROSTATE CANCER, unlike those in other tumor types, often seem to fly under the radar. And when there have been advances, they have tended to arrive in spurts, alternating with periods of relative quiet. When one stands back and considers the past decade, however, the expansion of therapeutic options for men diagnosed with this malignancy stands out.

Ten novel therapies have been approved for prostate cancer since 2010, a roster that includes immunotherapy, antiandrogens, and molecularly targeted agents. “It’s been an amazing run, to see all these new drugs approved for advanced prostate cancer with many, many more in development as we speak,” said Leonard G. Gomella, MD, FACS, a prostate cancer expert who has been a leader in the field since the 1980s.

In this issue of OncologyLive®, Gomella provides his insights into new drugs and treatment approaches that have recently entered clinical practice and several that are on the horizon. Importantly, Gomella notes that approvals for new drugs and indications in the past several years are shifting the focus to earlier points in the treatment timeline. This trajectory has improved outcomes for patients with other tumor types and we fervently hope the pattern repeats itself in prostate cancer.

Although much progress has been made in prostate cancer, the malignancy is still the most prevalent cancer and the second most deadly, after lung cancer, among men in the United States. There is a new focus on risk stratification and genomic analyses, a refreshing follow-up to the prostate-specific antigen screening controversies of the early 2000s, that we hope will enable more men to avoid undergoing radical prostatectomy.

We’ll hear much more about the latest treatment approaches for prostate cancer and other urologic malignancies during the New York GU™ 14th Annual Interdisciplinary Prostate Cancer Congress® and Other Genitourinary Malignancies conference. Physicians’ Education Resource®, LLC (PER®) will host the meeting virtually on March 12-13. For more information, visit https://bit.ly/3pJR4PR.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCE
**POWER FORWARD WITH CABOMETYX**

**THE ONLY TKI WITH SUPERIOR EFFICACY IN BOTH 1L AND 2L aRCC**

**FIRST- AND SECOND-LINE aRCC**

**CABOMETYX** (cabozantinib) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

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

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

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

- **Hypertension and Hypertensive Crisis:** CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension occurred in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

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

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

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

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

- **Impaired Wound Healing:** Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 3 weeks after major surgery and until adequate wound healing is observed. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.
The only TKI with superior PFS to sunitinib

**1L CABOSUN TRIAL**

The only TKI with superior OS in 2L aRCC

**2L METEOR TRIAL**

**PRIMARY ENDPOINT IN CABOSUN**

**MEDIAN PFS**

- CABOMETYX (n=79): 8.6 months
- Sunitinib (n=78): 5.3 months

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

HR=0.48 (95% CI: 0.31-0.74), P=0.00008

**SECONDARY ENDPOINT IN METEOR**

**MEDIAN OS**

- CABOMETYX (n=330): 21.4 months
- Everolimus (n=328): 16.5 months

HR=0.66 (95% CI: 0.53-0.83), P=0.00003

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

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

National Comprehensive Cancer Network (NCCN)®

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

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

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

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

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

**ADVERSE REACTIONS**

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

**DRUG INTERACTIONS**

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

**Strong CYP3A4 Inducers:** If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John’s wort.

**USE IN SPECIFIC POPULATIONS**

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

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

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

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

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

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

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

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Hemorrhage
Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 or 4 hemorrhagic events was 2% in CABOMETYX-treated patients in RCC and HCC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETYX to patients who have received a recent history of hemorrhage, including hemoptysis, hematoma, or melena.

5.2 Perforations and Fistulas
Fistulas, including fatal cases, occurred in 1% of CABOMETYX-treated patients. Gastrointestinal perforations involving fatal cases, occurred in 1% of CABOMETYX-treated patients.

5.3 Thrombotic Events
CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 2% of CABOMETYX-treated patients. Fetal thrombotic events occurred in CABOMETYX-treated patients.

Discontinue CABOMETYX in patients who develop Grade 3 or 4 gastrointestinal perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

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

Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

5.5 Diarrhea
Diarrhea occurred in 63% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 11% of patients treated with CABOMETYX.

Withhold CABOMETYX until improvement to Grade 3 or 4 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

5.6 Palmar-Plantar Erythrodysesthesia
Palmar-plantar erythrodysesthesia (PPE) occurred in 44% of patients treated with CABOMETYX. Grade 3 PPE occurred in 13% of patients treated with CABOMETYX.

Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

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

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

5.9 Impaired Wound Healing
Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

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

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

6.1 Clinical Trial Experience
The data described in the WARNINGS AND PRECAUTIONS section and below reflect exposure to CABOMETYX as a single agent in 409 patients with RCC enrolled in randomized, active-controlled trials (CABOSUN, METEOR) and 467 patients with HCC enrolled in a randomized, placebo-controlled trial (CELESTIAL).

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

Renal Cell Carcinoma METEOR
The safety of CABOMETYX was evaluated in METEOR, a randomized, open-label trial in which 331 patients with advanced renal cell carcinoma received CABOMETYX 60 mg once daily and 322 patients received everolimus 10 mg once daily until disease progression or unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator. The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving CABOMETYX and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

Adverse reactions which occurred in ≥ 25% of CABOMETYX-treated patients and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus. Adverse reactions leading to dose interruption occurred in 70% patients receiving CABOMETYX and in 50% patients receiving everolimus. Adverse reactions leading to study treatment discontinuation occurred in 10% of patients receiving CABOMETYX and in 10% of patients receiving everolimus.

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

The dose was reduced in 60% of patients receiving CABOMETYX and in 24% of patients receiving everolimus.

Twenty percent (20%) of patients receiving CABOMETYX 20 mg once daily as their lowest dose. The most frequent adverse reactions leading to dose reduction in patients treated with CABOMETYX were: diarrhea, PPE, fatigue, and hypertension. Adverse reactions leading to dose interruption occurred in 70% patients receiving CABOMETYX and in 50% patients receiving everolimus. Adverse reactions leading to study treatment discontinuation occurred in 10% of patients receiving CABOMETYX and in 10% of patients receiving everolimus.

Table 1. Adverse Reactions Occurring in ≥ 10% of Patients Treated with CABOMETYX in METEOR

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=331)</th>
<th>Everolimus (n=322)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage (%) of Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>74</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>56</td>
<td>9</td>
</tr>
<tr>
<td>Mental inflammation</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>Rash</td>
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<tr>
<td>Vascular</td>
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<tr>
<td>Hypertension</td>
<td>39</td>
<td>16</td>
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<tr>
<td>Blood and Lymphatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13</td>
<td>0</td>
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<tr>
<td>Anemia</td>
<td>11</td>
<td>1</td>
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<tr>
<td>Renal and Urinary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prognosis</td>
<td>12</td>
<td>2</td>
</tr>
</tbody>
</table>

1 One study conducted to everolimus received cabozantinib.
2 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
3 Includes the following terms: abdominal pain, abdominal pain upper, and abdominal pain lower
4 Includes the following terms: rash, rash erythematous, rash follicular, rash macular, rash papular, rash papulovesicular, genitai rash, intermittent leg rash, rash on scrotum and penis, rash maculo-papular, rash pruritic, contact dermatitis, dermatitis acneiform
5 Includes the following terms hypertension, blood pressure increased, hypertensive crisis, blood pressure fluctuation

The dose was reduced in 60% of patients receiving CABOMETYX and in 24% of patients receiving everolimus.

Twenty percent (20%) of patients receiving CABOMETYX 20 mg once daily as their lowest dose. The most frequent adverse reactions leading to dose reduction in patients treated with CABOMETYX were: diarrhea, PPE, fatigue, and hypertension. Adverse reactions leading to dose interruption occurred in 70% patients receiving CABOMETYX and in 50% patients receiving everolimus. Adverse reactions leading to study treatment discontinuation occurred in 10% of patients receiving CABOMETYX and in 10% of patients receiving everolimus.

The most frequent adverse reactions leading to permanent discontinuation in patients treated with CABOMETYX were decreased appetite (2%) and fatigue (1%).
Other clinically important adverse reactions (all grades) that were reported in <10% of patients treated with CABOMETYX included: wound complications (2%), confusion (<1%), pancreatitis (<1%), osteonecrosis of the jaw (<1%), and hepatitis cholestasis (<1%).

### Table 2. Laboratory Abnormalities Occurring in ≥ 25% Patients Who Received CABOMETYX in METEOR

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (n=331)</th>
<th>Everolimus (n=322)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>40</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>32</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>72</td>
<td>0</td>
</tr>
<tr>
<td>Increased triglycerides</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>28</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>29</td>
<td>1</td>
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<tr>
<td>Hypoglycemia</td>
<td>4</td>
<td>0</td>
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<td>Hypomagnesemia</td>
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<td>0</td>
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<tr>
<td>Hypoalbuminemia</td>
<td>26</td>
<td>6</td>
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<tr>
<td>Increased ALT</td>
<td>27</td>
<td>43</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>31</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>29</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anemia</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n = 78)</th>
<th>Sunitinib (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any Grade 3-4 Adverse Reaction</td>
<td>68</td>
<td>65</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Pain</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension1</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>Hypothension2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Angiopathy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased ALT3</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>4</td>
<td>3</td>
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<tr>
<td>Increased AST4</td>
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<td>3</td>
</tr>
<tr>
<td>Increased blood creatinine 2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Lymphopenia 1</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia 1</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
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<tr>
<td>Hypertension2</td>
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<td>1</td>
</tr>
<tr>
<td>Hypotension2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-plantar erythrodyssthesia</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Skin ulcer</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Blood and Lymphatic</td>
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<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
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<tr>
<td>Psychiatric</td>
<td></td>
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<tr>
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<tr>
<td>Confusional state</td>
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<td>1</td>
</tr>
<tr>
<td>Infections</td>
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<td></td>
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<tr>
<td>Lung infection</td>
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<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
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<td></td>
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<tr>
<td>Back pain</td>
<td>4</td>
<td>0</td>
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<tr>
<td>Bone pain</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Renal and Urinary</td>
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<td></td>
</tr>
<tr>
<td>Renal failure acute</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

- **ALT**: alanine aminotransferase, **AST**: aspartate aminotransferase, **GGT**: gamma glutamyl transferase.
- **Grade 3-4 (≥ 1%) Patients Who Received CABOMETYX in CASOSUN**

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=467)</th>
<th>Placebo (n=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any Grade 3-4 Adverse Reaction</td>
<td>68</td>
<td>65</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Pain</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension1</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>Hypothension2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Angiopathy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased ALT3</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Increased AST4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Increased blood creatinine 2</td>
<td>3</td>
<td>3</td>
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<tr>
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<tr>
<td>Thrombocytopenia 1</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Nervous System</td>
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<td></td>
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<tr>
<td>Syncope</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Vascular</td>
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<td></td>
</tr>
<tr>
<td>Hypertension2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hypotension2</td>
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<td>1</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
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<tr>
<td>Dyspnea</td>
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<td>0</td>
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<tr>
<td>Skin and Subcutaneous Tissue</td>
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<td></td>
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<tr>
<td>Palmar-plantar erythrodyssthesia</td>
<td>17</td>
<td>9</td>
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<tr>
<td>Rash2</td>
<td>12</td>
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<tr>
<td>Vascular</td>
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<td>Hypertension3</td>
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<tr>
<td>Investigations</td>
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<td></td>
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<tr>
<td>Weight decreased</td>
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<td>0</td>
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<tr>
<td>Nervous System</td>
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<tr>
<td>Dyspnea</td>
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<tr>
<td>Endocrine</td>
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<td>Hypothyroidism</td>
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<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
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<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>9</td>
<td>4</td>
</tr>
</tbody>
</table>

- **ALT**: alanine aminotransferase, **AST**: aspartate aminotransferase
- **Grade 3-4 (≥ 1%) Patients Who Received CABOMETYX in CELESTIAL**

### Hepatocellular Carcinoma

The safety of CABOMETYX was evaluated in CELESTIAL, a randomized, open-label, placebo-controlled trial in which 704 patients with advanced hepatocellular carcinoma were randomized to receive CABOMETYX 60 mg orally once daily (n=467) or placebo (n=237) until disease progression or unacceptable toxicity. The median duration of treatment was 3.8 months (range 0.1 – 37.3) for patients receiving CABOMETYX and 2.9 months (range 0.0 – 27.2) for patients receiving placebo. The population exposed to CABOMETYX was 81% male, 56% White, and had a median age of 64 years.

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

The median average daily dose was 35.8 mg for CABOMETYX. The dose was reduced in 62% of patients receiving CABOMETYX. 53% of patients required a reduction to 20 mg daily. The most frequent adverse reactions or laboratory abnormalities leading to dose reduction of CABOMETYX were: PPE, diarrhea, fatigue, hypertension, and increased AST. Adverse reactions leading to dose interruption occurred in 84% patients receiving CABOMETYX. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 16% of patients. The most frequent adverse reactions leading to permanent discontinuation of CABOMETYX were: fatigue (2%), nausea (2%), decreased appetite (1%), diarrhea (1%), and asthenia (1%).
In a pre- and postnatal study in rats, cabozantinib was administered orally from gestation day 10 through postnatal day 20. Cabozantinib did not produce adverse maternal toxicity or affect pregnancy, parturition or lactation of female rats, and did not affect the survival, growth or postnatal development of the offspring at doses up to 0.3 mg/kg/day (0.05-fold of the maximum recommended clinical dose).

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

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

Females

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

Infertility

Females and Males

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

8.4 Pediatric Use

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

Juvenile Animal Toxicity Data

Juvenile rats were administered cabozantinib at doses of 1 or 2 mg/kg/day from Postnatal Day 12 (comparable to less than 2 years in humans) through Postnatal Day 35 or 70. Mortalities occurred at doses ≥1 mg/kg/day (approximately 0.16 times the clinical dose of 60 mg/day based on body surface area). Hapactivity was observed at both doses tested on Postnatal Day 2. Targete were generally similar to those seen in adult animals, occurred at both doses, and included the kidney (nephropathy, glomerulonephritis), reproductive organs, gastrointestinal tract (cystic dilatation and hyperplasia in Brunner’s gland and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and whitening as well as effects on bones including reduced bone mineral content and density, phyeal hypertrophy, and decreased cortical bone also occurred at all dose levels. Recovery was not assessed at a dose of 2 mg/kg (approximately 0.32 times the clinical dose of 60 mg based on body surface area) due to high levels of mortality. At the low dose level, effects on bone parameters were partially resolved but effects on the kidney and epididymis/ testis persisted after treatment ceased.

8.5 Geriatric Use

In CABOSUN and METEOR, 41% of 409 patients treated with CABOMETYX were age 65 years and older, and 8% were 75 years and older. In CELESTIAL, 49% of 467 patients treated with CABOMETYX were age 65 years and older, and 15% were 75 years and older.

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

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

10 OVERDOSE

One case of overdosage was reported following administration of another formulation of cabozantinib; a patient inadvertently took twice the intended dose for 9 days. The patient suffered Grade 3 memory impairment, Grade 3 mental status changes, Grade 3 oedema, Grade 5 creatinine disturbance, Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

17 PATIENT COUNSELING INFORMATION

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

Hemorrhage: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage. Perforations and fistulas: Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during CABOMETYX treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking CABOMETYX. Thrombotic events: Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolus have been reported. Advise patients to contact their healthcare provider if new onset of dyspnea, chest pain, or localized limb edema occurs.

Hypertension and hypertensive crisis: Inform patients of the signs and symptoms of hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their healthcare provider if blood pressure is elevated or if they experience signs or symptoms of hypertension.

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

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

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

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

Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their healthcare provider for new onset or worsening neurological function.

Embryo-fetal toxicity: Advise females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy.

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

Drug Interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products. Inform patients to avoid grapefruit, grapefruit juice, and St. John’s wort.

1. CYP3A inducers: Cabozantinib is an inhibitor of CYP3A, may be a substrate or inducer of CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Avoid coadministration of CABOMETYX with strong CYP3A4 inhibitors. Avoid grapefruit or grapefruit juice which may also increase exposure of cabozantinib. Dosage of CABOMETYX can be reduced in patients taking strong CYP3A4 inhibitors if coadministration with strong CYP3A4 inhibitors cannot be avoided. Avoid grapefruit or grapefruit juice which may also increase exposure of cabozantinib.

2. CYP3A4 inducers: Strong CYP3A4 inducers can reduce exposure of cabozantinib. When coadministered with strong CYP3A4 inducers, reduce the dosage of CABOMETYX to avoid adverse drug reactions.

3. Strong CYP3A inhibitors: Strong CYP3A inhibitors can increase exposure of cabozantinib. Avoid coadministration of CABOMETYX with strong CYP3A4 inhibitors. If coadministration with strong CYP3A4 inhibitors cannot be avoided, avoid grapefruit or grapefruit juice which may also increase exposure of cabozantinib.

This brief summary is based on the CABOMETYX Prescribing Information.

Revision 02/2020

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It’s Time to Rethink 4 Unique Cancer Terms

by MAURIE MARKMAN, MD

The words we use in our communication with others, either verbally or in writing, may substantially affect the message being delivered. Of course, what is heard by the receiving party may not necessarily be identical to what we intend to convey. When one is dealing with the topic of cancer, its treatment and consequences, language that clinicians and members of the cancer research community use may have an even greater impact.

During 40 years of working in the oncology arena, I have witnessed the effects of certain words and terms commonly employed within the professional establishment whose unclear meaning and implications for patients, their families, and the general public may not have been adequately considered. Further, they may have resulted in unfortunate confusion rather than enlightenment. The following commentary highlights my perspective on several of these terms.

PALLIATIVE CARE

To palliate, “to make a disease or symptoms less severe or unpleasant without removing the cause” as defined in one English-language dictionary, is a critical goal of medicine, particularly for clinicians dealing with the manifestations of malignant disease. Critically, there is nothing in this definition that speaks to advanced, progressive, incurable, or end-stage illness. The term simply implies a specific therapeutic focus on directly controlling clinically meaningful symptoms, such as administering effective pain medications, rather than a more indirect effect resulting from the rapid or longer-term successful treatment of the cancer. This could include, for example, alleviating abdominal pain from the reduction of peritoneal carcinomatosis in response to cytotoxic drug delivery. Although such strategies have become increasingly relevant in cancer management, the term palliative care or, more specifically, a clinical palliative care service, has become essentially synonymous to many patients and their families with end-of-life care. It is not uncommon for patients with cancer to initially decline the opportunity to benefit from the expertise of a first-class palliative care team simply because they assume that this focus on symptom management is inconsistent with the goal of maximizing efforts to prolong survival. As a result, a strong argument can be made to educate both the public and our own clinical colleagues that, although optimal palliation of symptoms is essential when providing end-of-life care, this specific focus and expertise has the potential to be beneficial to patients throughout their cancer journey.

COMPLEMENTARY ALTERNATIVE MEDICINE

It is difficult to identify a clinically related concept that is more inaccurate, distorted, misleading, and potentially dangerous than that of complementary and alternative medicine (CAM). Complementary, or the more appropriate term used today—integrative—clearly implies the use of a wide variety of approaches designed to optimize the quality of life and enhance symptom management during the course of standard antineoplastic therapy. These strategies range from spiritual and behavioral medical support to far less fully understood interventions, such as acupuncture. The critical point here is that there is nothing “alternative” about such interventions because in this model of care they simply do not substitute for known effective anticancer therapeutics. Lumping these completely different concepts together in the expression CAM delivers an inappropriate message regarding the medically legitimate goals of integrative oncology care. Take, for example, one rather bizarre report that appeared in a peer-reviewed journal several years ago. Investigators examined records in the National Cancer Database of 1,901,815 patients treated from January 1, 2004, through December 31, 2013, and identified individuals “who received complementary medicine,” as self-reported by 258 patients, or 0.01% of the total population in this database. The authors concluded that these patients were more likely to refuse conventional cancer treatment and experience inferior survival compared with those who did not list an interest in this approach to cancer care.1 In addition to the profoundly
inadequate sample size for drawing any meaningful conclusions, the authors’ decision to consider individuals interested in alternative approaches to conventional therapy as being equivalent to those desiring an integrative strategy focused on enhancing quality of life while undergoing state-of-the-art oncology care either unintentionally or intentionally distorts facts. The term CAM simply needs to be discarded, never again to be used by cancer specialists, other clinicians, or members of the research community.

**PRECISION CANCER MEDICINE**

As relevant as the term *precision cancer medicine* has become in describing a focus of modern anti-neoplastic drug delivery, there remains a serious issue with the way in which many in the oncology community are using it. Precision cancer medicine refers to a specific goal of our treatment paradigm: to become ever more precise in favorably impacting cancer-relevant molecular targets, measured by improved objective response rates, time to disease progression, or overall survival. The term does not refer to a specific time or event, such that one can declare treatment has achieved a state of being optimally “precise.” The fact that a particular trial of a theorized relevant drug-target combination has failed to reveal the benefits of that approach does not signify a failure of the process of precision cancer medicine. Rather, this outcome serves as an example of how the process should work, discarding approaches that have not demonstrated meaningful benefit while continuing to examine other novel strategies that will hopefully, following appropriate clinical investigation, achieve the desired goal.

**CURE**

There is probably no more powerful word in all of oncology, and no potential question associated with more fear following the diagnosis of cancer, than when a patient or family member inquires: “Will I or my loved one be cured?” Of course, as all oncologists know, the answer to this question can be quite complex, depending on the tumor type, disease stage, and other considerations. The point here is that even when “cure” is a realistic—or at least not irrational—goal of therapy, achieving this clinical state, with important exceptions such as nonmelanoma skin cancers, is something one only knows with reasonable medical certainty at some point in the future. Depending on the natural history of the specific malignancy in question, this may represent a period of many years into that future. Providing an honest but also encouraging and hopeful response is one of the first important challenges facing treating oncologists as they begin to assist patients through their cancer survivorship journey.

**REFERENCE**

Better is home to New Jersey’s best cancer center

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.
Nivolumab Plus Cabozantinib Gains Approval for Advanced RCC
The armamentarium for the frontline treatment of patients with advanced renal cell carcinoma (RCC) has expanded with the approval of nivolumab (Opdivo) plus cabozantinib (Cabometyx).

The approval was based on findings from the phase 3 CheckMate 9ER trial (NCT03141177), which demonstrated that the doublet led to a 49% reduction in the risk of disease progression or death, significantly improved overall survival, and doubled objective response rates compared with sunitinib (Sutent).

The median OS had not yet been reached in either treatment arm, translating to a 40% reduction in the risk of death with the investigational doublet (HR, 0.60; 95% CI, 0.40-0.89; P = .0010).

See Drug Spotlight on page 25 for more information.


Nivolumab Gets Decision Date for Resected Esophageal/GEJ Cancer
The FDA is expected to make a decision by May 20 on the supplemental biologics license application for nivolumab (Opdivo) for use as an adjuvant treatment for patients with resected esophageal or gastroesophageal junction (GEJ) cancer following neoadjuvant chemoradiation treatment.

The decision to grant a priority review designation was based on data from the phase 3 CheckMate 577 trial (NCT02743494), which demonstrated that nivolumab resulted in a statistically significant and clinically meaningful improvement in disease-free survival compared with placebo in patients with resected esophageal or GEJ cancer after neoadjuvant chemoradiation.

Findings from the global, double-blind, placebo-controlled trial showed that the median disease-free survival with adjuvant nivolumab was 22.4 months (95% CI, 16.6-34.0) versus 11.0 months (95% CI, 8.3-14.3) with placebo (HR, 0.69; 95% CI, 0.56-0.86; P < .0001).

This benefit was observed across all prespecified subgroups analyzed, including age, sex, race, ECOG performance status, disease stage at initial diagnosis, tumor location, histology, pathologic lymph node status, and PD-L1 expression.

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

Narsoplimab Is Under Consideration for HSCT Supportive Care
The investigational, fully human IgG4 monoclonal antibody narsoplimab (OMS721) is set to undergo priority review for the treatment of hematopoietic stem-cell transplant–associated thrombotic microangiopathy (HSCT-TMA).

The FDA’s decision was based on data from a phase 2 trial (NCT02222545) in which narsoplimab induced complete responses and led to improved laboratory markers and promising 100-day survival rates in patients with HSCT-TMA.

Patients in the total population treated with narsoplimab (n = 28) achieved a complete response rate of 54% (95% CI, 34%-72%). In 23 patients treated per study protocol who had received 4 weeks or more of dosing, the overall response rate was higher, at 65% (95% CI, 43%-84%). Additionally, the 100-day survival rate following HSCT-TMA diagnosis was 68% in all patients who received treatment with narsoplimab; in patients treated per study protocol, this rate was 83%. The 100-day survival rate was highest in 15 patients who were identified to be responders to treatment, at 93%.

The FDA is expected to make a decision on the application by July 17.

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

Decision Deadline Is Set for Retifanlimab for Anal Cancer
Retifanlimab (INCMGA0012) has been granted a priority review by the FDA for a biologics license application for the treatment of adult patients with locally advanced or metastatic squamous cell carcinoma of the anal canal (SCAC) who are intolerant of or have progressed on platinum-based chemotherapies.

Findings from the phase 2 POD1UM-202 trial (NCT03597295) showed that the investigational, humanized anti–PD-1 monoclonal antibody displayed promising activity in patients with platinum-refractory SCAC (n = 94), including those positive for HIV.

The agent elicited an objective response rate of 13.8% (95% CI, 7.6%-22.5%) per independent central review using RECIST v1.1 criteria, with a 1.1% complete response rate, a 12.8% partial response rate, and a 35.1% stable disease rate. Just under half (45.7%) of patients experienced disease progression. The disease control rate in these patients was 48.9%, and the median duration of response was 9.5 months. Further, at a median follow-up of 7.1 months, the median progression-free survival was 2.3 months (95% CI, 1.9-3.6), and the median overall survival was 10.1 months (95% CI, 7.9-not estimable).

The FDA is scheduled to issue a decision on the application by July 25.

TO READ MORE, VISIT https://bit.ly/2Mw0H69.

Tepotinib Gains Approval for METex14-Altered Metastatic NSCLC
Data from the phase 2 VISION trial (NCT02864492) has provided the basis for the FDA to grant accelerated approval to tepotinib (Tepmetko) for the treatment of adult patients with metastatic non–small cell lung cancer (NSCLC) harboring MET exon 14 skipping alterations.

Findings from the trial showed that the MET inhibitor induced an objective response rate (ORR) of 43% (95% CI, 32%-56%) among 69 treatment-naïve patients per blinded independent review committee using RECIST v1.1 criteria. Moreover, the median duration of response (DOR) with the agent was 10.8 months (95% CI, 6.9-not estimable).

Among the 83 previously treated patients included in the trial, the ORR was also 43% (95% CI, 33%-55%) and the median DOR was 11.1 months (95% CI, 9.5-18.5). Progression-free survival data were presented at the International Association for the Study of Lung Cancer 2020 World Conference on Lung Cancer. The median progression-free survival was 8.5 months (95% CI, 6.8-11.3) for treatment-naïve patients and 10.9 months (95% CI, 8.2-12.7) for those who had prior treatment.

Additionally, responses were analyzed according to whether the presence of a MET exon 14 skipping mutation was detected on liquid or tissue biopsy. ORRs in the liquid (n = 66) and tissue biopsy groups (n = 60) were 48% (95% CI, 36%-61%) and 50% (95% CI, 37%-63%), respectively.

IN THE TREATMENT OF RELAPSED REFRactory MULTIPLE MYELOMA
IN COMBINATION WITH POMALIDOMIDE AND DEXAMETHASONE (Pd)

ACHIEVE GREATER OUTCOMES FOR YOUR PATIENTS

SARCLISA is an anti-CD38 therapy proven to deliver superior PFS (median PFS of 11.53 months with SARCLISA + Pd vs 6.47 months with Pd alone, HR=0.596, 95% CI: 0.44, 0.81, P=0.0010). SARCLISA also demonstrated a significant increase in ORR (60.4% with SARCLISA + Pd [95% CI: 52.2%, 68.2%] vs 35.3% with Pd alone [95% CI: 27.8%, 43.4%], P<0.0001)*

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
Preferred Category 1 recommendation for isatuximab-irfc (SARCLISA)

Isatuximab-irfc (SARCLISA), in combination with pomalidomide and dexamethasone, is a Preferred Category 1 option for previously treated multiple myeloma by the National Comprehensive Cancer Network® (NCCN®)

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.

*ORR included sCR, CR, VGPR, and PR. sCR, CR, VGPR, and PR were evaluated by an IRC using the IMWG response criteria.1
CR=complete response; IMWG=International Myeloma Working Group; IRC=independent response committee; mAb=monoclonal antibody; NCCN=National Comprehensive Cancer Network; ORR=overall response rate; PFS=progression-free survival; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.

Indication

SARCLISA (isatuximab-irfc) is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

Important Safety Information

CONTRAINDICATIONS
SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients.

WARNINGS AND PRECAUTIONS
Infusion-Related Reactions
Infusion-related reactions (IRRs) have been observed in 39% of patients treated with SARCLISA. All IRRs started during the first SARCLISA infusion and resolved on the same day in 98% of the cases. The most common symptoms of an IRR included dyspnea, cough, chills, and nausea. The most common severe signs and symptoms included hypertension and dyspnea.

Please see Important Safety Information throughout, and accompanying brief summary of full Prescribing Information.
Choose SARCLISA + Pd to Offer Improved Outcomes to More Patients vs Pd Alone

Studied in the phase 3 ICARIA-MM trial, which included patients with poor prognostic factors

Based on the ICARIA-MM trial, SARCLISA + Pd is a treatment choice for patients with relapsed refractory multiple myeloma

- Who have received at least 2 prior therapies, including lenalidomide and a PI
- Who may have renal impairment (creatinine clearance <60 mL/min/1.73 m²), high cytogenetic risk, or a history of COPD or asthma
- Who may have poor performance status or are ≥75 years of age
- Who are refractory to lenalidomide, a PI, or both

STUDY DESIGN: ICARIA-MM (NCT02990338), a multicenter, open-label, randomized, phase 3 study, evaluated the efficacy and safety of SARCLISA in 307 patients with relapsed refractory multiple myeloma who had received at least 2 prior therapies, including lenalidomide and a PI. Patients received either SARCLISA 10 mg/kg administered as an IV infusion in combination with Pd (n=154) or Pd alone (n=153), administered in 28-day cycles until disease progression or unacceptable toxicity. SARCLISA was given weekly in the first cycle and every 2 weeks thereafter. Pomalidomide 4 mg was taken orally once daily from day 1 to day 21 of each 28-day cycle. Low-dose dexamethasone (orally or IV) 40 mg (20 mg for patients ≥75 years of age) was given on days 1, 8, 15, and 22 for each 28-day cycle. PFS was the primary endpoint; ORR and OS were key secondary endpoints. PFS results were assessed by an IRC, based on central laboratory data for M-protein, and central radiologic imaging review using the IMWG criteria. Median follow-up was 11.6 months.

PATIENT CHARACTERISTICS: The median patient age was 67 years (range, 36 to 86), and 20% of patients were ≥75 years of age. Ten percent of patients entered the study with a history of COPD or asthma. The proportion of patients with renal impairment (creatinine clearance <60 mL/min/1.73 m²) was 34%. The ISS stage at study entry was I in 37%, II in 36%, and III in 25% of patients. Overall, 20% of patients had high-risk chromosomal abnormalities at study entry: del(17p), t(4;14), and t(14;16) were present in 12%, 8%, and 2% of patients, respectively. The median number of prior lines of therapy was 3 (range, 2 to 11). All patients received a prior PI, all patients received prior lenalidomide, and 56% of patients received prior stem cell transplantation; the majority of patients (93%) were refractory to lenalidomide, 76% to a PI, and 73% to both an immunomodulator and a PI.

COPD=chronic obstructive pulmonary disease; ISS=International Staging System; IV=intravenous; OS=overall survival; PI=proteasome inhibitor.

Important Safety Information (cont’d)

Infusion-Related Reactions (cont’d)

To decrease the risk and severity of IRRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H₂ antagonists, diphenhydramine or equivalent, and dexamethasone. Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade 1 or 2 reactions, interrupt SARCLISA infusion and provide appropriate medical support. If symptoms improve, restart SARCLISA infusion at half of the initial rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally. In case symptoms do not improve or recur after interruption, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA if a grade 3 or higher IRR occurs and institute appropriate emergency medical management.
SARCLISA + Pd Extended Median PFS to ~1 Year

Superior PFS with SARCLISA + Pd vs Pd alone

The median duration of treatment was 41 weeks with SARCLISA + Pd vs 24 weeks with Pd. At a median follow-up time of 11.6 months, 43 patients (27.9%) receiving SARCLISA + Pd and 56 patients (36.6%) receiving Pd had died. Median OS was not reached for either treatment group at interim analysis. The OS results at interim analysis did not reach statistical significance.

SARCLISA + Pd showed a significant increase in ORR

<table>
<thead>
<tr>
<th>SARCLISA + Pd (n=154)</th>
<th>Pd (n=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>60.4%</strong> ORR</td>
<td><strong>35.3%</strong> ORR</td>
</tr>
<tr>
<td><strong>31.8%</strong> ≥VGPR</td>
<td><strong>8.5%</strong> ≥VGPR</td>
</tr>
<tr>
<td>35 days</td>
<td>Median time to first response among responders 58 days</td>
</tr>
</tbody>
</table>

*ORR included sCR, CR, VGPR, and PR. ORR: SARCLISA + Pd (95% CI: 52.2%, 68.2%), Pd (95% CI: 27.8%, 43.4%).

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

**Neutropenia**

SARCLISA may cause neutropenia. Neutropenia (reported as laboratory abnormality) occurred in 96% of patients and grade 3–4 neutropenia occurred in 85% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd). Febrile neutropenia occurred in 12% of patients and neutropenic infections, defined as infection with concurrent grade ≥3 neutropenia, occurred in 25% of patients treated with Isa-Pd. The most frequent neutropenic infections included those of upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%).

Please see Important Safety Information throughout, and accompanying brief summary of full Prescribing Information.
Important Safety Information (cont’d)

Neutropenia (cont’d)
Monitor complete blood cell counts periodically during treatment. Consider the use of antibiotics and antiviral prophylaxis during treatment. Monitor patients with neutropenia for signs of infection. In case of grade 4 neutropenia, delay SARCLISA dose until neutrophil count recovery to at least 1.0 x 10^9/L, and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCLISA are recommended.

Second Primary Malignancies
Second primary malignancies were reported in 3.9% of patients in the SARCLISA, pomalidomide, and dexamethasone (Isa-Pd) arm and in 0.7% of patients in the pomalidomide and dexamethasone (Pd) arm, and consisted of skin squamous cell carcinoma (2.6% of patients in the Isa-Pd arm and in 0.7% of patients in the Pd arm), breast angiosarcoma (0.7% of patients in the Isa-Pd arm), and myelodysplastic syndrome (0.7% of patients in the Isa-Pd arm). With the exception of the patient with myelodysplastic syndrome, patients were able to continue SARCLISA treatment. Monitor patients for the development of second primary malignancies.

Laboratory Test Interference

Interference with Serological Testing (Indirect Antiglobulin Test)
SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). In ICARIA–multiple myeloma (MM), the indirect antiglobulin test was positive during SARCLISA treatment in 67.7% of the tested patients. In patients with a positive indirect antiglobulin test, blood transfusions were administered without evidence of hemolysis. ABO/RhD typing was not affected by SARCLISA treatment. Before the first SARCLISA infusion, conduct blood type and screen tests on SARCLISA-treated patients. Consider phenotyping prior to starting SARCLISA treatment. If treatment with SARCLISA has already started, inform the blood bank that the patient is receiving SARCLISA and SARCLISA interference with blood compatibility testing can be resolved using dithiothreitol–treated RBCs. If an emergency transfusion is required, non–cross–matched ABO/RhD–compatible RBCs can be given as per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests
SARCLISA is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M–protein. This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein.

Embryo-Fetal Toxicity
Based on the mechanism of action, SARCLISA can cause fetal harm when administered to a pregnant woman. SARCLISA may cause fetal immune cell depletion and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for at least 5 months after the last dose. The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

ADVERSE REACTIONS
The most common adverse reactions (≥20%) were neutropenia (laboratory abnormality, 96% Isa-Pd vs 92% Pd), infusion–related reactions (38% Isa–Pd vs 0% Pd), pneumonia (31% Isa–Pd vs 23% Pd), upper respiratory tract infection (57% Isa–Pd vs 42% Pd), and diarrhea (26% with Isa–Pd vs 19% Pd). Serious adverse reactions occurred in 62% of patients receiving SARCLISA. Serious adverse reactions in >5% of patients who received Isa–Pd included pneumonia (26%), upper respiratory tract infections (7%), and febrile neutropenia (7%). Fatal adverse reactions occurred in 11% of patients (those that occurred in more than 1% of patients were pneumonia and other infections [3%]).

USE IN SPECIAL POPULATIONS
Because of the potential for serious adverse reactions in the breastfed child from isatuximab–irfc administered in combination with Pd, advise lactating women not to breastfeed during treatment with SARCLISA.

Please see accompanying brief summary of full Prescribing Information.

SARCLISA® Rx Only (isoxлимab-ибп) injection, for intravenous use

Brief Summary of Prescribing Information

1. Development of SARCLISA

SARCLISA is indicated, in combination with pomalidomide and dexamethasome, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

• Administer re-infusion infusions at the same dose as previously

• The infusion solution should be administered within 48 hours of preparation.

2.2 Recommended Premedications

• Pre-medicate patients prior to SARCLISA infusion (see Warnings and Precautions (5.3)).

2.3 Dose Modifications

• The infusion solution should be administered for a period of 30 minutes, the infusion rate may be increased to the initial rate of 50 mL/hour every 30 minutes then increased by 100 mL/hour every 30 minutes

2.4 Preparation

• Prepare the solution for infusion using aseptic technique as follows:

2.5 Administration

• Administer the infusion solution by intravenous infusion using an intravenous tubing infusion set (in PE, PVC with or without DEHP, polybutadiene [PBD], or polyurethane [PU]) with a 0.22 micron in-line filter (polyethersulfone [PES], polysulfone, or nylon).

• The infusion solution should be administered for a period of 30 minutes then increased by 100 mL/hour every 30 minutes.

Table 1: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Days of Treatment</th>
<th>Dosing schedule</th>
</tr>
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<tbody>
<tr>
<td>Cycle 1</td>
<td>Days 1, 8, 15, and 22 (weekly)</td>
<td>250 mL or 50 mL/hour</td>
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<td>Cycle 2 and beyond</td>
<td>Days 1, 15 (every 2 weeks)</td>
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</tr>
<tr>
<td>Cycle 2 and beyond</td>
<td>Days 1, 15 (every 2 weeks)</td>
<td>200 mL/hour</td>
</tr>
</tbody>
</table>

4 CONTRAINDICATIONS

SARCLISA is contraindicated in patients with severe hypersensitivity reactions, or to any of its excipients (see Warnings and Precautions (5.1)).

5 WARNINGS AND PRECAUTIONS

5.1 Neutropenia

• Neutropenia is a well-known adverse effect of SARCLISA. The most common severe signs and symptoms included fever and infection with neutropenia delay SARCLISA dose until neutrophil count recovery to at least 1.0 × 10^9/L, and provide supportive care with growth factors (if used in institutional guidelines). No dose reductions of SARCLISA are recommended.

5.2 Second Primary Malignancies

Second primary malignancies were reported in 3.9% of patients who received SARCLISA, pomalidomide and dexamethasone.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions from SARCLISA are also described in other sections of the labeling:

• Neutropenia (see Warnings and Precautions (5.1)).

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6.1 Clinical Trials Experience

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

6.2 Clinical Laboratory Tests

• Hematology: Absolute neutrophil count ≥1.5 × 10^9/L

• Chemistry: Serum creatinine clearance ≥30 mL/min (MDRD formula), and AST and/or ALT ≤3 × ULN.

6.3 Embryo-Fetal Toxicity

SARCLISA is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein. This interference may impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein (see Drug Interactions (7.1)).

6.4 Interference with Serological Testing (Indirect Antiglobulin Test)

• Interference with blood compatibility testing can be resolved using diolite-coated-treated RBCs. If an emergency transfusion is required, non–cross-matched ABO/Rh-compatible RBCs may be given as per local blood bank practices (see Drug Interactions (7.1)).

7.1 Drug Interactions

Do not administer SARCLISA infusion solution concomitantly with pomalidomide and dexamethasome, according to the schedule in Table 1 (see Clinical Studies (14) in the full prescribing information). Administration of pomalidomide with dexamethasone may cause fetal immune cell depletion and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for at least 5 months after the last dose (see Use in Specific Populations (8.1, 8.3)). The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

7.2 Pregnancy

• SARCLISA is a pregnancy category B drug (see Use in Specific Populations (8.1, 8.3)).

• Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for at least 5 months after the last dose (see Use in Specific Populations (8.1, 8.3)).

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The most common adverse reactions (≥20%) were neutropenia, infusion-related reactions, pneumonia, upper respiratory tract infection, and diarrhea.

Table 3 summarizes the adverse reactions in ICARIA-MM.

### Table 3: Adverse Reactions (≥10%) in Patients Receiving SARCLISA, Pomalidomide, and Dexamethasone with a Difference Between Arms of ≥5% Compared to Control Arm in ICARIA-MM Trial

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (is-Pd)</th>
<th>Pomalidomide + Dexamethasone (Pd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>38</td>
<td>1.3</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>57</td>
<td>7</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17</td>
<td>5</td>
</tr>
</tbody>
</table>

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*Pneumonia includes atypical pneumonia, bronchopulmonary aspergillosis, pneumonia, pneumonia haemophilus, pneumonia influenza, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, candida pneumonia, pneumonia bacterial, haemophilus infection, lung infection, pneumonia fungal, and pneumocystis jiroveci pneumonia.

**Upper respiratory tract infection includes bronchitis, bronchitis viral, chronic sinusitis, fungal pharyngitis, influenza-like illness, laryngitis, macropharyngeal fever (virus infection), pharyngitis, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tracheitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.

**Dyspnea is defined as dyspnea, dyspnea exertional, and dyspnea at rest.

Table 4 summarizes the laboratory abnormalities in ICARIA-MM.

### Table 4: Treatment Emergent Hematology Laboratory Abnormalities in Patients Receiving is-Pd Treatment versus Pd Treatment – ICARIA-MM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (is-Pd) (N=152)</th>
<th>Pomalidomide + Dexamethasone (Pd) (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Anemia</td>
<td>151</td>
<td>49</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>145</td>
<td>37</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>141</td>
<td>64</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>127</td>
<td>58</td>
</tr>
</tbody>
</table>

Description of Selected Adverse Reactions

**Infusion-related reactions**

In ICARIA-MM, infusion-related reactions (defined as adverse reactions associated with the SARCLISA infusion, with an onset typically within 24 hours from the start of the infusion) were reported in 58 patients (36%) treated with SARCLISA. All patients who experienced infusion-related reactions, experienced them during the 1st infusion of SARCLISA, with 3 patients (2%) also having infusion-related reactions at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 infusion-related reactions were reported in 3.9%, Grade 2 in 32%, Grade 3 in 1.3%, and Grade 4 in 1.3% of the patients. Signs and symptoms of Grade 3 or higher infusion-related reactions included dyspnea, hypotension, and bronchospasm. The incidence of infusion interruptions because of infusion-related reactions was 29.6%. The median time to interruption was 55 minutes.

In a separate study (TGC 14079 Part B) with SARCLISA 10 mg/kg administered via a 250 mL fixed-volume infusion in combination with Pd, infusion-related reactions (all Grade 2) were reported in 45% of patients, at the first administration, the day of the infusion. Overall, the infusion-related reactions of SARCLISA 10 mg/kg administered as a 250 mL fixed-volume infusion were similar to that of SARCLISA as administered in ICARIA-MM.

### 6.2 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 this study described below with the incidence in antibodies in other studies or to other isatuximab-irfc products may be misleading.

In ICARIA-MM, no patients tested positive for antidrug antibodies (ADA). Therefore, the neutralizing ADA status was not determined. Overall, across 6 clinical studies in multiple myeloma (MM) with SARCLISA single-agent and combination therapies including ICARIA-MM (N=554), the incidence of treatment-emergent ADAs was 2.3%. No clinically significant differences in the pharmacokinetics, safety, or efficacy of isatuximab-irfc were observed in patients with ADAs.

### 7 DRUG INTERACTIONS

#### 7.1 Laboratory Test Interference

Interference with Serological Testing

SARCLISA, an anti-CD38 antibody, may interfere with blood bank serologic tests with false positive reactions in indirect antibody tests (indirect Coombs tests), antibody detection (screening tests), antibody identification panels, and anti-human globulin crossmatch in patients treated with SARCLISA (see Warnings and Precautions 5.4). Interference with Serum Protein Electrophoresis and Immunofluorescence Tests

SARCLISA may be incidentally detected by serum protein electrophoresis and immunofluorescence assays used for the monitoring of M-protein and may interfere with accurate response classification based on International Myeloma Working Group (IMWG) criteria (see Warnings and Precautions 5.4).

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

SARCLISA can cause fetal harm when administered to a pregnant woman. The assessment of isatuximab-irfc-associated risks is based on the mechanism of action and data from target antigen CD38 knockout animal models (see Data). There are no available data on SARCLISA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse outcomes. Animal reproduction toxicology studies have not been conducted with isatuximab-irfc. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, miscarriage, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The combination of SARCLISA and pomalidomide is contraindicated in pregnant women because pomalidomide administer birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy. Pomalidomide is only available through a REMS program.

**Clinical Considerations**

Fetal/neonatal reactions

Immunoglobulin G1 monoclonal antibodies are known to cross the placenta. Based on its mechanism of action, SARCLISA may cause depletion of fetal CD38-positive immune cells and decreased bone density. Refer administration of live vaccines to neonates and infants exposed to SARCLISA in utero until a hematologic evaluation is completed.
Nivolumab/Cabozantinib Combo Joins RCC Lineup

by JASON HARRIS

PATIENTS WITH METASTATIC RENAL cell carcinoma (RCC) have a new frontline treatment alternative following FDA approval of the combination of nivolumab (Opdivo) plus cabozantinib (Cabometyx) combination. The doublet induced a 40% reduction in the risk for death compared with sunitinib (Sutent).¹

The combination pairing the immune checkpoint inhibitor (ICI) nivolumab with the VEGF inhibitor cabozantinib was approved on January 22, 2021, based on findings from the phase 3 CheckMate 9ER trial (NCT03141177). The regimen improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) versus sunitinib in patients with RCC.

“It’s going to be another option for frontline clear cell RCC. It’s not the only combination that is approved, but I think there are some distinctions, especially with the quality-of-life data,” said principal investigator Toni K. Choueiri, MD. He is the director of the Lank Center for Genitourinary Oncology and a senior physician at Dana-Farber Cancer Institute, as well as the Jerome and Nancy Kohlberg Chair and Professor of Medicine at Harvard Medical School, both in Boston, Massachusetts.

The approval follows a trend of combination therapies incorporating ICIs for first-line RCC therapy. In less than 2 years, the FDA has approved frontline combinations of axitinib (Inlyta), a VEGF inhibitor, with the ICIs pembrolizumab (Keytruda) or avelumab (Bavencio). Dual therapy with the ICIs nivolumab and ipilimumab (Yervoy), a CTLA-4 inhibitor, also is approved for previously untreated intermediate- or poor-risk advanced RCC.²

The nivolumab/cabozantinib option, Choueiri said, has shown activity across all risk groups in the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). Overall, at a median follow-up of 18.1 months, the median PFS with the combination was 16.6 months (95% CI, 12.5-24.9) versus 8.3 months (95% CI, 7.0-9.7) with sunitinib monotherapy (HR, 0.51; 95% CI, 0.41-0.64; P < .0001). The median OS had not yet been reached in either treatment arm (HR, 0.60; 98.8% CI, 0.40-0.89; P = .0010).

Previous study findings showed that nivolumab promotes antitumor responses by preventing cancer from evading immune detection. Cabozantinib, on the other hand, has antiangiogenic and immunomodulatory properties thought to counteract tumor-induced immunosuppression. Both agents are approved in monotherapy settings in RCC.

In CheckMate 9ER, investigators randomly assigned 651 patients with advanced clear cell RCC to first-line nivolumab in combination with cabozantinib (n = 323) or sunitinib (n = 328). To be eligible for enrollment, patients had to be treatment naïve and have advanced or metastatic disease with a clear cell component.

Results from CheckMate 9ER, presented during the 2020 European Society for Medical Oncology Virtual Congress, demonstrated that the doublet induced activity across several subgroups. These spanned age, sex, PD-L1 expression, bone metastases, IMDC risk groups, and geographic region.

The doublet also showed a favorable safety profile. Incidence of any-grade and high-grade treatment-related adverse effects (TRAEs) were similar between the 2 arms. Of patients who received cabozantinib or nivolumab, 15.3% reported TRAEs that resulted in treatment discontinuation compared with 8.8% of those in the sunitinib arm.¹

Nineteen percent of participants in the investigational arm required corticosteroids due to immune-associated toxicities, with 4% of them needing corticosteroids for at least 30 days. Choueiri said that the rate of complete treatment discontinuation due to AEs and use of steroids, especially after 14 and 28 days, was generally low for the combination. Moreover, one should expect a greater incidence of toxicities with 2 drugs rather than with 1, he said.

“One thing to mention is that the dose of cabozantinib in CheckMate 9ER is not the same dose when we use cabozantinib as monotherapy,” Choueiri said. “The approved indication of cabozantinib monotherapy in first-line and second-line RCC is 60 mg orally once a day. With the combination, it’s 40 mg once a day. Even with that, the efficacy end points were met. It’s possible that the toxicity could be lower and the quality of life better because of that adjustment, [compared with] a full dose of sunitinib.”

Additionally, Choueiri noted, the nivolumab/cabozantinib combination resulted in improved health-related quality-of-life (QOL) scores compared with sunitinib. Health-related QOL was maintained over time with the doublet versus sunitinib, which had a consistent deterioration per Functional Assessment of Cancer Therapy (FACT)-Kidney Symptom Index (FKSI)-19 total score and on the FKSI disease-related symptom subscale. The differences between arms were found to be significant at most time points over 91 weeks.¹

“QOL is the voice of the patient. We can grade toxicities as much as we want—these are questionnaires that the patients answer about how they feel,” Choueiri said. “It is still very hard to extrapolate and say, ‘This is the only superior combination for QOL against sunitinib versus the other combination,’” simply because the combinations have not been compared head-to-head.

He continued: “There is not one questionnaire and one QOL metric. There are many, and there isn’t a real hardcore consensus on what constitutes a clinically meaningful QOL,” he said. “Also, you may not have general improvement in QOL, but there are [important] elements that are part of it, like fatigue, that could be different. So you’ll have to dig into this very closely.”

Investigators will present patient-reported outcomes from this trial at the 2021 Genitourinary Cancers Symposium in February.

Moving forward, Choueiri said, patients with RCC will have “an embarrassment of riches” in terms of treatment options, giving rise to questions on sequencing.

“The question is, if someone went with 1 regimen of VEGF-IO [immuno-oncology], could they switch to another VEGF-IO knowing that it does have OS benefit, but now [they are] treated so it’s not the same indication?” Choueiri said. “It’s going to be a bit complicated in RCC. That’s why our group and several others remain interested in targets and drugs outside the VEGF receptor and the PD-1/PD-L1 and CTLA-4 blockade.”

REFERENCES


![Toni K. Choueiri, MD](image)
PIVOTAL CLINICAL TRIAL

The phase 3 CheckMate 9ER (NCT03141177) was a randomized, open-label trial involving 651 patients with previously untreated advanced or metastatic RCC. Patients were randomized to receive either nivolumab 240 mg intravenously every 2 weeks plus cabozantinib 40 mg orally daily or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle.

BASELINE PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Median age (years, range)</th>
<th>Nivolumab and cabozantinib (n = 323)</th>
<th>Sunitinib (n = 328)</th>
</tr>
</thead>
<tbody>
<tr>
<td>62 (29-90)</td>
<td>19% Favorable</td>
<td>21% Poor</td>
</tr>
<tr>
<td>58%</td>
<td>58% Intermediate</td>
<td>57%</td>
</tr>
<tr>
<td>23%</td>
<td>22% Poor</td>
<td>21%</td>
</tr>
<tr>
<td>IMDC risk category</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Most common site of metastasis (%)

- Nivolumab and cabozantinib: 74% (lung), 40% (bone), 24% (lymph node), 23% (kidney), 16% (brain)
- Sunitinib: 76% (lung), 40% (bone), 22% (lymph node), 16% (kidney), 10% (brain)

Number of sites with target/nontarget lesions

- Nivolumab and cabozantinib: 80% (1 site), 20% (≥ 2 sites)
- Sunitinib: 78% (1 site), 21% (≥ 2 sites)

SELECT ADVERSE EFFECTS IN > 15% OF PATIENTS IN CHECKMATE 9ER

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Nivolumab + cabozantinib (n = 320)</th>
<th>Sunitinib (n = 320)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>64% Grades 1-4</td>
<td>47% Grades 1-4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5% Grades 1-4</td>
<td>8% Grades 1-4</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>44% Grades 1-4</td>
<td>24% Grades 1-4</td>
</tr>
<tr>
<td>Palmoplantar erythrodysesthesia syndrome</td>
<td>40% Grades 1-4</td>
<td>8% Grades 1-4</td>
</tr>
</tbody>
</table>

REFERENCES

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Should All Elderly Patients With Newly Diagnosed Multiple Myeloma Receive Monoclonal Antibodies?

by MARC J. BRAUNSTEIN, MD, PhD

COMBINATION ANTIMYELOMA REGIMENS containing monoclonal antibodies and a robust pipeline of novel targeted agents are some of the contributing factors generating a new wave of optimism in the field of multiple myeloma.1 However, elderly or frail patients with multiple myeloma may not be eligible for certain treatments, such as adoptive T-cell therapies and bispecific antibodies, that hold the potential for serious adverse events (AEs) in this population. Therefore, inclusion of novel agents, such as monoclonal antibodies, as part of induction for elderly patients with newly diagnosed multiple myeloma offers the potential to improve outcomes in this challenging population.

Considering the median age of diagnosis of multiple myeloma is 69 years, and that most study results showing a benefit for consolidation with stem cell transplantation (SCT) have been limited to patients 70 years or younger, it is imperative to provide treatments that both prolong survival and maintain quality of life for older patients with newly diagnosed multiple myeloma.2 Beyond biological age and performance status, geriatric assessments can provide quantitative measures of fitness that predict survival and treatment toxicities, thereby stratifying patients for more or less intensive therapies.3,4

Because most phase 3 studies of novel agents have used conventional enrollment criteria based on factors such as performance status, SCT candidacy, and baseline organ function, rather than stratifying according to frailty measures, questions remain as to whether a one-size-fits-all approach is suitable for all patients who are elderly/transplant ineligible. Nevertheless, recent randomized controlled studies of up-front triplet and quadruplet induction regimens including monoclonal antibodies have consistently demonstrated durability and tolerability in elderly patients with multiple myeloma.

COMBINATIONS DEMONSTRATE EARLY EFFICACY

The 2014 publication of data from the FIRST trial (NCT00689936) showed a survival benefit with continuous lenalidomide (Revlimid) and dexamethasone compared with the combination of melphalan, prednisone, and thalidomide (Thalomid) in transplant-ineligible patients ranging from 40 to 92 years (median overall survival [OS], 59 vs 49 months; \( P = .0023 \)).5,6 These data demonstrated that prolonged exposure to novel agents was effective and tolerable in elderly patients.

Further, building on data that showed the efficacy of the monoclonal antibody daratumumab (Darzalex), particularly in elderly patients with relapsed multiple myeloma,7,8 recent study findings have similarly demonstrated a benefit of up-front daratumumab in this population. According to data from the phase 3 ALCYONE study (NCT02195479) of patients with newly diagnosed multiple myeloma ineligible for SCT aged 40 to 93 years,9 the combination of daratumumab with bortezomib (Velcade), melphalan, and prednisone (D-VMP) was superior to VMP alone. Updated survival analysis showed a 78% versus 68% OS at 36 months (HR, 0.60; \( P = .0003 \)), again preserved in patients 75 years or older.10 Grade 3 or 4 hematologic AEs were similar between treatment groups, although respiratory tract infections were more common in the D-VMP arm (11.3% vs 4%).10

"It is imperative to provide treatments that both prolong survival and maintain quality of life for older patients with newly diagnosed multiple myeloma."
In the phase 3 MAIA study (NCT02252172) comparing the combination of daratumumab, lenalidomide, and dexamethasone (D-Rd) to Rd in patients with a median age of 73 years (range, 45-90), a 42% reduction in progression was observed with D-Rd in the 44% of patients 75 years or older enrolled in the trial (HR, 0.58; 95% CI, 0.44-0.87). Although the OS analysis has yet to be read out, the median progression-free survival (PFS) at 47.9 months was not reached in the D-Rd group compared with 34.4 months with Rd (HR, 0.54).

The benefit of up-front daratumumab was not preserved in patients with high-risk cytogenetics; however, considering this was a relatively smaller subgroup of patients, it may take more time to see a benefit than has been demonstrated with daratumumab regimens in the relapsed setting. Health-related quality-of-life measures in the MAIA study were superior with D-Rd, with no statistical differences in cognitive decline between either arm at 12 months. In addition, in my practice, I favor giving subcutaneous daratumumab plus carfilzomib (Kyprolis), lenalidomide, and dexamethasone in the GMMG-CONCEPT trial (NCT03104842), which examined patients with newly diagnosed high-risk disease, showed a 100% overall response rate, with all 4 patients who were ineligible for SCT achieving a very good partial response.

**TABLE.** Trial Snapshot

<table>
<thead>
<tr>
<th>Trial [ClinicalTrials.gov identifier]</th>
<th>Study arms</th>
<th>Median follow-up</th>
<th>Survival outcome</th>
<th>ORR</th>
<th>MRD negativity (10^{-7} by NGS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCYONE (NCT02195479)</td>
<td>D-VMP vs VMP</td>
<td>40 months</td>
<td>Median OS: 78% vs 68% (HR, 0.60)</td>
<td>91% vs 74%</td>
<td>28% vs 7%</td>
</tr>
<tr>
<td>MAIA (NCT02252172)</td>
<td>D-Rd vs Rd</td>
<td>47.9 months</td>
<td>Median PFS: NR vs 34.4 months (HR, 0.54)</td>
<td>93% vs 82%</td>
<td>31% vs 10%</td>
</tr>
</tbody>
</table>

**TABLE**

**Phase 3 Studies of Up-Front Daratumumab in Patients With Newly Diagnosed Transplant-Ineligible MM**

**In the context of the largely positive data for up-front monoclonal antibody regimens in elderly patients with multiple myeloma**, should all elderly patients receive these regimens? Although tolerability may be acceptable, the patients with higher frailty measures who were excluded from the phase 3 studies shown in **TABLE 1** might be better served with less intensive regimens. For example, frail patients with multiple myeloma may not be able to travel to an infusion center for the initial weekly daratumumab induction period over 2 months. In addition, the annual cost of treatment for a regimen such as DRD (daratumumab, lenalidomide, and dexamethasone) is estimated to be $290,000, which will be even higher with quadruplet regimens, particularly when expanded over a several-year period. Because both D-VMP and D-Rd regimens have category 1 National Comprehensive Cancer Network recommendations, insurers are likely to cover these treatments, although potential financial toxicity should be a consideration, particularly for elderly patients receiving regimens containing oral agents.

Marc J. Braunstein, MD, PhD, is an assistant professor in the Department of Medicine at NYU Long Island School of Medicine and course codirector of the Hematology-Oncology System at NYU Langone Health.

For a full list of references, see the article at https://bit.ly/2N3x10k.
OncologyLive® traces the impact of COVID-19 from bedside to bench.

Expert Gives Nod to COVID-19 Vaccines for Patients With Cancer

by GINA MAURO

PATIENTS WITH CANCER SHOULD strongly consider being vaccinated to prevent coronavirus disease 2019 (COVID-19) and to reduce the risks associated with the virus, despite the potential of having a weakened immune system, according to David E. Cohn, MD.

“We know that patients with cancer have a higher rate of contracting COVID-19, and they also have a higher rate of severe complications or death from COVID-19 if they were to get it,” Cohn said. “To me, that is very important information on how an individual [patient with] cancer should think about protecting him or herself to minimize the chance that they’re going to have a major complication from this disease.”

The FDA granted emergency use authorizations to the Pfizer-BioNTech COVID-19 vaccine and the Moderna COVID-19 vaccine, as the first vaccines to prevent COVID-19 in individuals 16 and 18 years and older, respectively, in December 2020!

In an interview with OncologyLive®, Cohn, chief medical officer at The Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, director of gynecologic cancer research, associate director of the Gynecologic Oncology Fellowship Program, and the Stuart M. Sloan-Larry I. Copeland MD Chair in Gynecologic Oncology at The Ohio State University in Columbus, discussed how to approach COVID-19 vaccination in patients with cancer.

A lot of the research that was the basis for these vaccines had been in the works for years. Therefore, there was a massive head start to get to this point, and that’s the important thing [to remember] about how we can be here so quickly; the research had been [ongoing] for years. The FDA has been evaluating this research and has looked at the short-term safety. [Although] we don’t have long-term safety data, there is nothing that would make us believe that there is anything inherently risky about these vaccines. The second misconception surrounds how patients [should] be expected to respond to the vaccines. This includes patients with cancer and those with cancer who have had treatment and have a reduced immune system. Therefore, the question becomes whether you have a vaccine that a patient can have a response to or whether their lack of immune response is going to lead them to not have any effect from that vaccine.

However, what is known is that even individuals who have been heavily treated for cancer still have the capacity to mount an immune response. Most importantly, some level of immunity to COVID-19 is better than none. Right there is the key—any patient who has cancer should be vaccinated, unless there’s an absolute contraindication for them to be vaccinated.
Could you share some background about the technology of these vaccines?

When you think about the technology behind an mRNA vaccine or the general process for any vaccine, you introduce something [that] is recognized by the body as being foreign, and then the body can mount an immune response to it. That immune response is then going to be durable, meaning it may last for months or years or more than that. That is the general principle for all vaccines. This technology is using mRNA, a small piece of the genetic material of the spike protein of COVID-19 itself.

Someone described the technology as Snapchat. In Snapchat, you send a photograph, and then that photograph is deleted from somebody’s phone, for example—so that it’s not durable. The mechanism is that the delivery is the Snapchat—it’s there and then it’s gone. However, the lasting impact of that photograph can be quite durable, and that’s the hope with the immunity as well.

I like that analogy because it does demonstrate that you can do something, which you can see and feel, but then it goes away very quickly. That’s the technology where you have the mRNA that’s wrapped in a certain type of compound, a lipid, that allows it into the body and then it is disintegrated very quickly. However, the immunity process is far longer lasting.

Are you looking at certain criteria when discussing vaccine eligibility for your patients with cancer?

The criteria that we use about who should or should not be vaccinated is fairly simple. There are certain contraindications to the vaccine, and those are individuals who have an anaphylaxis or severe allergic reaction to previous mRNA vaccines or to other medications. That’s certainly one thing that you want to talk to your health care provider about, to ensure that there’s no way that you could get a vaccine.

Beyond that, in general, patients should be vaccinated. I talk to my patients about the fact that I’ve been vaccinated; as someone who cares for patients with cancer, I want to make sure that I minimize my personal risk. Then, the second piece is

NCCN Releases COVID-19 Vaccination Guidance for Patients With Cancer

by COURTNEY MARABELLA

ALL PATIENTS WITH ACTIVE CANCER or with active, recent, or planned cancer treatment should be considered highest priority to receive one of the coronavirus disease 2019 (COVID-19) vaccines that have been granted emergency use authorization from the FDA, according to guidance released by the National Comprehensive Cancer Network (NCCN). 1

The NCCN’s COVID-19 Vaccine Committee—which is comprised of hematology and oncology experts who specialize in infectious diseases, vaccine development and delivery, medical ethics, and health information technology—released recommendations to assist cancer-care providers in making more informed decisions to better protect their patients from the virus. The recommendations decided upon were based on all available evidence and expert consensus. The NCCN’s top recommendations include the following:

- Patients with cancer should be prioritized for vaccination because they are included in CDC priority group 1b or 1c and should be immunized once the vaccine is available.
- Immunization is recommended for all patients on active therapy, with the understanding that limited safety and efficacy data are available.
- Reasons for delay of vaccines in this population are comparable to those for the general public, such as recent exposure to the virus as well as other cancer-specific factors. Immunization should be delayed for at least 3 months after hematopoietic cell transplantation or engineered cellular therapy, such as chimeric antigen receptor T-cell therapy, to maximize the effectiveness of the vaccine.
- All caregivers and household contacts of patients with cancer should also be vaccinated when the option is available to them.

Specifically, patients with solid tumors who are receiving cytotoxic chemotherapy, targeted therapy, checkpoint inhibitors and other immunotherapy, or radiation should receive the vaccine as it is available. Those undergoing major surgery should schedule vaccination a few days separated from the procedure. Patients with hematologic malignancies—including those on long-term maintenance therapy, such as targeted agents for chronic lymphocytic leukemia or myeloproliferative neoplasms, and those who experience marrow failure from disease and/or therapy expected to have limited or no recovery—should receive the vaccine when it is available.

It is further recommended that patients receiving intensive cytotoxic chemotherapy for hematologic malignancy delay vaccination until absolute neutrophil count recovery.

In the event of limited vaccine supply, the NCCN specified in their guidance that patients with active cancer on treatment, including those on hematopoietic and cellular therapy, those planning to begin treatment, and those who received treatment less than 6 months prior, should be among the first to be immunized. Patients receiving hormonal therapy are the only exception to this.

The guidance also recommended that providers consider additional risk factors in patients who could put them at higher risk for COVID-19 infection, such as advanced age (65 years and older), other comorbidities (eg, chronic pulmonary, cardiovascular or renal disease), and social and demographic factors (including poverty, limited access to health care, and underrepresented minorities).

The guidance from the NCCN also acknowledged that, although trial data have demonstrated that the COVID-19 vaccine is safe and effective among the general population, the efficacy of these vaccines in patients with cancer is still relatively unknown.

Vaccine trials have shown data indicating a decrease in the incidence of COVID-19 infection and complications, but it is still unclear whether these vaccines fully prevent infection and subsequent transmission. As such, it is recommended that patients with cancer, as well as their caregivers and household contacts, continue to wear masks and follow social distancing and other COVID-19 preventive measures even after vaccination.

The NCCN COVID-19 Vaccine Committee will continue to meet regularly to refine the recommendations for these and other issues.

For a full list of references, see the article at https://bit.ly/3oARuqA.
that we know that certain chemotherapy drugs have the same polyethylene glycol, which is one of the compounds that is part of the mRNA vaccine.

Therefore, for patients with cancer, if you’ve had an allergic reaction to certain chemotherapy drugs, there may also be a reason to not be vaccinated with this mRNA technology. Again, you will need to speak with your health care provider to make sure that there’s the appropriate scrutiny being taken to make sure that you’re not able to be vaccinated. If that’s the case, there are new technologies or other types of vaccine technology on the horizon that hopefully will be authorized for emergency use by the FDA that [these patients] may be eligible for, if not the mRNA vaccines.

Right now, it’s just a matter of how we sequence patients because the vaccines currently are still a relatively scarce resource. Therefore, if we’re in a position to have more vaccines, we may then use certain types of allergic reactions as a determination as to what type of vaccine someone should have.

[We need to consider], for patients with cancer in particular, that there might be an optimal time during their chemotherapy cycles that they should be vaccinated. If you have 2 vaccines that are required, which have the mRNA technology that’s existing, then maybe if there’s a vaccine that’s authorized with 1 vaccine [dose], that could actually be optimal for patients with cancer. You would only have to plan 1 vaccine around chemotherapy and not have separate vaccinations.

**What if a patient is undergoing a different cancer treatment? Do any of these interfere with the vaccine?**

Different kinds of treatments, whether a small molecule inhibitor, antibody therapy, cytotoxic chemotherapy, immunotherapy, or radiation, have different effects. Any patient with cancer should speak to their oncologist about whether there’s an optimal time for them to receive the vaccine, and a lot of it depends upon their history, their immune system, and the expectation for what the future holds for their treatments as well. That will determine the appropriate timing for vaccination.

**What are the key adverse effects associated with the vaccine that should be stressed to patients?**

The message about vaccine adverse effects is that they are most likely going to happen. That is going to be a sore arm or some redness or warmth in the vaccination site, and that’s just your body providing that reaction to the mRNA, to the vaccine itself.

Severe complications are very, very rare. Although these are the ones that we read about in the newspaper or hear about on the radio—that make the news—that is not what defines the general status of vaccination. It seems to be very safe.

It seems that the second vaccine [dose] may have more adverse effects than the first because that’s the goal. It’s priming the body, and then it’s boosting the immunity with a second vaccine. You can think about timing the vaccine around your daily life so that you’re not in a position of experiencing a sore arm or even a low-grade temperature at a time when you need to be maximally functional.

**Do you have any advice for other health care professionals who are having these conversations about the vaccine with their patients, especially those who are apprehensive or concerned about long-term adverse effects?**

These conversations are very important to have. Certainly, engaging in shared decision-making with a patient is critically important because patients are going to come in with their own conceptions about whether they want to be vaccinated or not. It’s important to make sure that we’re having these conversations that are directed toward their goals as well.

There are a lot of resources out there. [The American Society of Clinical Oncology] has great patient-facing resources....The American College of Obstetricians and Gynecologists also have patient-facing resources [regarding] breastfeeding and pregnancy with a vaccine. Make sure to leverage all of the resources that are out there, educate ourselves as much as we can as providers of cancer care, but also make sure that we [share] decision-making with our patients so that we are achieving their goals as well.

ARE YOU THINKING DEEP ENOUGH IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA?

Relapse is expected, but deep response could be too\textsuperscript{1,2}

With each relapse, multiple myeloma becomes increasingly difficult to control. As the disease progresses, very few patients (less than 5\%) experience a deep response.\textsuperscript{1,2} However, evidence suggests a deep response may be associated with improved PFS and OS.\textsuperscript{1,3} 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

\textsuperscript{1}OS=overall survival, PFS=progression-free survival

Gomella Lauds Breakthroughs in GU Cancers

by LARRY HANOVER

A RECENT WAVE OF drug approvals for treating prostate cancer in earlier disease states coupled with genomic advances may help pave the way for a shift toward handling the malignancy as a chronic condition, according to Leonard G. Gomella, MD, FACS.

Starting with the February 2018 approval of apalutamide (Erleada), the FDA has carved out indications for patients with nonmetastatic castration-resistant prostate cancer (CRPC) and castration-sensitive prostate cancer, moving the use of androgen receptor (AR)-targeting agents earlier in the therapeutic paradigm.1,2

Instead of focusing on treating men with late-stage prostate cancer, medical and urologic oncologists now have new options to attack the disease earlier in its progression, Gomella noted in an interview with OncologyLive®.

“One of the concepts we talk about in prostate cancer is a shift to the left,” he said, referring to the treatment timeline. “Studies are investigating traditional agents used in advanced disease states and moving them to earlier disease states. In theory, [this would] suppress the progression of prostate cancer so instead of a life-threatening disease it becomes a chronically managed disease like diabetes or hypertension—that’s where a lot of the research is going,” Gomella said.

“The field is investigating drugs that may alter that trajectory of prostate cancer by doing more work on the cancer’s unique genetics and understanding the genetic triggers that you may be able to interact with earlier in the course of the disease to either slow progression or even prevent it from metastasizing. Or, once it’s metastasized, leave it there in a holding pattern.”

Gomella, a widely recognized expert in urologic cancers, is the Bernard W. Godwin Jr Professor of Prostate Cancer, and chair of the Department of Urology and senior director clinical affairs at Sidney Kimmel Cancer Center at Thomas Jefferson University in Philadelphia, Pennsylvania.

He will share his insights into new developments in the field during the New York GU™ 14th Annual Interdisciplinary Prostate Cancer Congress® and Other Genitourinary Malignancies conference. Physicians’ Education Resource®, LLC (PER®) will host the meeting virtually on March 12-13.

Gomella will serve as program cochair, joined by Daniel P. Petrylak, MD, professor of medicine (medical oncology) and of urology and cofounder of Cancer Signaling Networks at Yale Cancer Center in New Haven, Connecticut, as well as a 2017 Giants of Cancer Care® award winner.

The first day of the conference will feature presentations on urothelial carcinoma and renal cell carcinoma, and the second will focus primarily on prostate cancer.

Gomella’s involvement with New York GU™ reflects the leadership role that he has established during his nearly 40-year career in urology. Gomella helped pioneer the use of molecular analyses in prostate cancer through the development of reverse transcriptase-polymerase chain reaction for prostate-specific antigen (PSA) to detect circulating prostate cancer micrometastases in the early 1990s.3 This work is considered the earliest concept of the “liquid biopsy” being used today. In addition, he led the urology effort for the 2017 Philadelphia...
Prostate Cancer Consensus Conference that resulted in the first multidisciplinary guidelines on genetic testing for prostate cancer. 4

“Dr Gomella has been a major force in urologic oncology,” said Robert Dreicer, MD, director of solid tumor oncology in the Division of Hematology/Oncology at the University of Virginia (UVA) School of Medicine and deputy director of the UVA Cancer Center in Charlottesville, Virginia.

“He works in all the major urologic malignancies, but his work in prostate cancer involves translational genomics. He’s been a major contributor with genomics in predicting the risk of localized disease in the role of intervention. And he pioneered multidisciplinary management of prostate cancer. He’s really in the forefront of urologic oncology in 2021.”

KEY DEVELOPMENTS IN PROSTATE CANCER

This year’s New York GU ™ meeting will be brimming with new information about best practices and emerging research for each cancer type on the agenda, Gomella said. For example, Dreicer will discuss integrating genetic testing for prostate cancer. 4

Several groundbreaking developments in prostate cancer that occurred during 2020 will be covered. These include approvals for the PARP inhibitors rucaparib (Rubraca) and olaparib (Lynparza), the first oral molecularly targeted therapies for this tumor type; relugolix (Orgovyx), the first oral gonadotropin-releasing hormone (GnRH) receptor antagonist; and Gallium 68 PSMA-11 (Ga 68 PSMA-11), the first drug for positron emission tomography (PET) imaging of prostate-specific membrane antigen (PSMA)-positive lesions in men with prostate cancer.

The 2 recent PARP approvals for prostate cancer, which occurred within a 5-day period in May 2020, “are opening up a whole new spectrum of oral agents for the management of advanced prostate cancer,” Gomella said.

rucaparib demonstrated an objective response rate of 44% (95% CI, 31%-57%) in 62 patients with measurable disease. Participants received rucaparib 600 mg orally twice daily along with a GnRH analog or had prior bilateral orchiectomy.

Olaparib is indicated for adult patients with metastatic CRPC harboring a germline or somatic mutation in a homologous recombination repair (HRR) gene, including BRCA1/2, who have progressed following prior treatment with enzalutamide (Xtandi) or abiraterone acetate (Zytiga). The drug was approved based on data from the phase 3 PROfound study (NCT02987543), in which patients were randomized 2:1 to olaparib at 300 mg twice daily (n = 256) or investigator’s choice of therapy (n = 131). As in the rucaparib trial, all participants also received a GnRH analog or had prior bilateral orchiectomy.

Participants were divided into 2 cohorts based on mutation status: cohort A for those with mutations in BRCA1/2 or ATM and cohort B for those with mutations in 12 other genes associated with HRR. Radiological progression-free survival (rPFS) in cohort A, the primary end point of the study, was a median of 7.4 months (95% CI, 6.2-9.3) among those who received olaparib versus 3.6 months (95% CI, 1.9-3.7) for patients who received investigator’s choice of therapy (HR, 0.34; 95% CI 0.25-0.47; P < .0001). The median overall survival was 19.1 months (95% CI, 17.4-23.4) with olaparib versus 14.7 (95% CI, 11.9-18.8) with investigator’s choice (HR, 0.69; 95% CI, 0.50-0.97; P = .0175). The median rPFS for olaparib in cohorts A plus B also was higher than for standard therapy (5.8 vs 3.5 months; HR, 0.49; P < .0001).

“PARP inhibitors interfere with the ability of the malignant prostate cancer cell’s DNA HRR mutations to repair itself and continue to grow, so they are a very effective tool,” Gomella said. “PARP inhibitors are considered third-, or fourth-line therapies; these men must have failed other standard therapeutic interventions for metastatic castrate-resistant prostate cancer to be eligible for olaparib or rucaparib.”

The population of patients with advanced disease who could be eligible for PARP therapy represents a significant subset. Study findings indicate that the prevalence of germline mutations in genes regulating DNA repair processes in men with metastatic prostate cancer is at least 11.8%, including 5.3% with BRCA2 and 0.9% with BRCA1 mutations. In men with localized high-risk disease, the incidence of HRR genes was 6%. 7

Additionally, the FoundationOne Liquid CDx assay has been approved as the companion diagnostic to detect relevant mutations for both PARP inhibitors. The next-generation sequencing tool is a liquid biopsy capable of analyzing circulating cell-free DNA isolated from plasma derived from peripheral whole blood of patients with cancer. 8

“Developments in biomarkers and genetics have been explosive,” said Gomella, who will be giving a presentation on this topic. “We now have circulating tumor DNA that can be evaluated in patients with prostate cancer to determine genetic susceptibility to new medications. This is a big breakthrough.”

Relugolix, approved in December 2020...
for patients with advanced prostate cancer, is the most recent arrival on the scene. The FDA based its decision on findings from the phase 3 HERO trial (NCT03085095), in which relugolix demonstrated superiority over leuprolide (Lupron) in terms of sustained testosterone (T) suppression through 48 weeks, T recovery following discontinuation, and a 50% reduction in major adverse cardiovascular events (MACE). Leuprolide, a luteinizing hormone-releasing hormone (LHRH) agonist, is administered subcutaneously, as are other androgen deprivation therapy options.9,10

The sustained castration rate with relugolix was 96.7% (95% CI, 94.9%-97.9%) versus 88.8% (95% CI, 84.6%-91.8%) with leuprolide, for a 7.9 percentage point difference between the therapies. T recovery to at least 280 ng/dL at 90 days was 54.0% with relugolix versus 3.0%, and the cumulative incidence of MACE was 2.8% versus 5.6%, respectively.9,10

Gomella said that relugolix will be an important part of discussion at New York GU™ given its recent addition to the treatment paradigm. “The HERO trial demonstrated that relugolix had excellent suppression of testosterone,” Gomella said. “And, as an oral antagonist, it showed a very rapid decline in testosterone in the studies. It’s another brand-new option in prostate cancer. Urologists are going to have to become familiar with this new agent and how to choose the optimum patient for the use of this oral agent for androgen deprivation therapy. While urologists are very comfortable with injectable agents to lower testosterone, this formulation is something that we’re not used to using in daily practice.”

Relugolix also has the advantage of coming in tablet form, as opposed to degarelix (Firmagon), the only other FDA-approved GnRH receptor antagonist, which is administered monthly as a subcutaneous injection in the abdominal region. “Since relugolix is an antagonist, you do not see a surge in testosterone at week 2 that you see with the LHRH agonists,” Gomella said. “So there is some benefit to using an antagonist in certain settings.”

In terms of imaging, the impact of the FDA approval of Ga 68 PSMA-11 in December 2020 will not be widely available in clinical practice but it is a noteworthy development nonetheless, Gomella said. The radioactive diagnostic agent, which is administered as an intravenous injection, is indicated for patients with suspected prostate cancer metastases who are considered potentially curable by surgery or radiation therapy. It also is indicated for patients with suspected recurrence based on rising PSA levels.12

As it stands now, Ga 68 PSMA-11 is only approved for use at the University of California (UCLA), Los Angeles and UCLA, San Francisco, where studies have taken place. Outside of a clinical trial at other centers, the California sites are the only locations authorized in the United States for the diagnostic, although Gomella said it has been available for some time in Europe, Australia, and New Zealand.

“PSMA PET scan is designed to pick up metastases from prostate cancer at a very low PSA level, and a very low volume of metastases compared to traditional agents such as MRIs, CAT scans, and bone scans. While other PET agents for prostate cancer are available, PSMA PET imaging is something that’s going to be commonly utilized as it becomes more widely available in the United States,” Gomella said.

In a comparative study (NCT03515577), UCLA investigators evaluated 50 patients with biochemical recurrence after a radical prostatectomy with low PSA levels with the standard 18F-fluciclovine PET-CT scan and the PSMA PET-CT. The PSMA scan detected recurrences of prostate cancer in 56% of scans, compared with 26% with the fluciclovine scan, for an odds ratio of 4.8 (95% CI, 1.6-19.2; P = .0026).11 “Hopefully, there will be other centers around the United States that will be eligible to jump on their FDA approval,” Gomella said.

A related approach under investigation is the use of PSMA-based theragnostics. This approach combines therapeutic and diagnostic functions in the management of metastatic prostate cancer, Gomella said. One such agent under study is lutetium-177-labeled PSMA-617 (LuPSMA), a radionuclide therapy that significantly improved PSA response compared with cabazitaxel (Jevtana) in men with metastatic CRPC whose disease progressed after docetaxel treatment (N = 200) in the phase 2 TheraP study (NCT03392428). The reduction in PSA, defined as 50% or greater from baseline, was 66% (95% CI, 56%-75%) in the LuPSMA arm versus 37% (95% CI, 27%-46%) with cabazitaxel, for an absolute difference of 29% (95% CI, 16%-42%; P < .0001).14

“Using the theragnostics approach, a prostate cancer avid antibody finds the cell, and there’s a radioactive payload that’s associated with it,” Gomella said. “And once that antibody binds to the malignant cell, a radioisotope such as lutetium-177 kills the cancer cells.”

**UROTHELIAL CARCINOMA**

Gomella said there will be several topics on tap at New York GU™ involving advances in bladder cancer. These include treating patients with high-risk, non-muscle invasive bladder cancer (NMIBC) who are not responsive to BCG with pembrolizumab (Keytruda).
In January 2020, the FDA approved pembrolizumab monotherapy in this setting for NMIBC with carcinoma in situ with or without papillary tumors. The approval was based on findings from the KEYNOTE-057 trial (NCT02625961) involving 96 patients who had undergone transurethral resection of bladder tumor (TURBT) to remove all resectable disease. The complete response rate for these patients, defined as negative results for cystoscopy with TURBT or biopsies as applicable, was 41% (95% CI, 31%-51%), with a median duration of response of 16.2 months (range, 0.0-30.4+), with 46% of the respondents (n = 18) exhibiting a response for 12 months or longer. “What was particularly fascinating about this approval is the fact that this is a systemic therapy for non-muscle invasive bladder cancer,” Gomella said. “This is not used as an intravesical agent.”

Emerging therapies generating excitement in NMIBC settings include nadofaragene firadenovec (also known as rAd-IFNα/Syn3), an adenovirus vector-based gene therapy that targets urothelial cells, as an alternative to radical cystectomy in BCG-nonresponsive NMIBC.

In a January 2021 publication, Gomella and colleagues reported findings from a phase 3 multicenter trial (NCT02773849), supported by the Society of Urologic Oncology, of nadofaragene firadenovec in BCG-nonresponsive NMIBC. Within 3 months of the first dose, the therapy elicited a complete response in 53.4% of 103 patients (n = 55) with carcinoma in situ with or without concomitant high-grade Ta or T1 disease. Of these patients, 45.3% (n = 25) maintained their response at 12 months.

“Clinical trials showed that this was a very effective intravesical gene therapy for non-muscle invasive bladder cancer. This is another breakthrough development in NMIBC,” Gomella said.

The FDA is currently evaluating a biologics license application for nadofaragene firadenovec, according to FerGene Inc, the company developing the drug.

Another development that experts will discuss at New York GU™ is mitomycin gel (Jelmyto), which was approved in April 2020 for patients with low-grade upper tract urothelial cancer (UTUC) based on data from the single-arm, phase 3 OLYMPUS trial (NCT02793128). Of the 71 patients treated with mitomycin gel, 58% achieved a complete absence of tumor lesions 3 months after receiving therapy; 19 of the 41 respondents maintained a complete response at 12 months (median duration, not reached; range, 0-8.8+ months). The therapy has implications in the management of bladder cancer; Gomella said approximately 10% to 15% of patients with bladder cancer can develop UTUC and 20% to 30% of those diagnosed with UTUC may develop bladder cancer.

“At cool temperature, this agent is liquid but when warm it becomes a gel. This is injected into the upper urinary tract through the bladder,” Gomella said. “This agent has allowed us to maintain the renal unit in many patients with low-grade urothelial carcinoma who otherwise may have no option other than taking their kidney out. So this is another novel urothelial/bladder cancer development that we’ve had over the past year.”

A HISTORY OF TEAMWORK

Throughout his career, Gomella has emphasized a team spirit in oncology care. One of his most prominent efforts in recent years has been leading the urology effort in the Philadelphia Prostate Cancer Consensus, which brings together experts from throughout the United States and abroad to discuss the role of genetic testing in prostate cancer. In 2017, the consensus meeting produced the first comprehensive set of recommendations to guide physicians on when to offer men genetic consultation. Two years later, they reconvened a 2019 consensus in Philadelphia to consider challenges in the execution and education of prostate cancer germline testing.

The 2017 meeting, which took place just a few years after the growing recognition that some prostate cancers were related to genetic risk, was an important milestone, said Philip W. Kantoff, MD, a 2014 Giants of Cancer Care® award winner and chair of the Department of Medicine at Memorial Sloan Kettering Cancer Center in New York, New York.

“That was a very important meeting, not as much scientifically as educationally, because a lot of the people who were invited were urologists who are not as familiar with the importance of germline testing,” Kantoff said. “It has really taken off with regard to testing for more aggressive forms of prostate cancers and looking for DNA repair abnormalities that might be significant.”

Genomic testing is one of the most exciting areas of development in Gomella’s eyes. “Identification of these genetic alterations is giving us another alternative pathway to treat these men who ultimately develop metastatic castrate-resistant prostate cancer,” he said.

More than 20 years before the consensus conferences, Gomella was busy launching other collaborative projects. In 1993, he teamed up with a Philadelphia Inquirer science writer to publish the first book specifically addressing prostate cancer for the public, Recovering From Prostate Cancer. In the mid-1990s, he introduced a multidisciplinary clinic at the Sidney Kimmel Cancer Center where patients are able to meet with radiation, medical, and urologic surgical specialists during the same visit. Part of the visit includes evaluation for potential clinical trial participation. Most of the men coming through the multidisciplinary clinic have early prostate cancer and are considering the choice of either active surveillance or intervention, usually with radiation or surgery.

“We’re very proud of this multidisciplinary approach,” Gomella said. “We’ve been doing this approach at the Sidney Kimmel Cancer Center since way back in 1996. We’ve found it to be an amazing experience. We don’t know of any other center that’s been doing it as long as we have. Many other centers have started to do it because it’s a very patient- and family-friendly approach to prostate cancer. We’re all at the same place at the same time to talk to the patient and their family, and then give them our best recommendation for the treatment pathway they should start on.”

In 2014, the multidisciplinary clinic began incorporating an introduction to prostate cancer genetic testing, another first in the field. Patients and their families receive an overview of whether pursuing genetic testing is something they should consider after their initial treatment has begun, Gomella said. The goal is to identify patients who have a genetic predisposition not just to prostate
cancer but other related inherited malignan-
cies. This includes breast and ovarian cancer
in female relatives as well as pancreatic
cancer, melanoma, or male breast cancer in
the patient or his close family members.

“Testing family members of a patient with
prostate cancer is a concept known as cascade
testing,” Gomella said. “Is this something that
perhaps their children should be aware of, that
they might have an inherited genetic predispo-
sition to these related groups of cancer? This
requires a very up-close-and-personal dis-
cussion with the patient or family. While most
patients with prostate cancer do not appear to
habor an inherited genetic risk, 15% to 20% of
men may benefit from further genetic evalua-
tion. We believe thoughtful genetic testing and
counseling is the future of precision medicine
in all of cancer care.”

Another point of pride is the scientific
research that Gomella and colleagues have
conducted into molecular biomarkers.

“When it comes to a basic science discov-
ery, something that usually does not get a lot
of attention is something that I’m particu-
larly proud of. In 1992, we described the first
molecular test to identify circulating prostate
cells in the blood. I think this really
laid the groundwork for others who started
to investigate whether we can use molecular
tests to identify circulating tumor cells and
other molecular targets in the blood.”

The research was ahead of its time, he said.
“Over the past 25 years, the basic molecular
work we did has been eclipsed and expanded
dramatically. It was probably too early;
we and others who joined in this prelim-
nary prostate cancer work didn’t really
fully understand the biology of molecular
test blood testing.”

FIGHTING THE GOOD FIGHT

Although Gomella has been a driving force in
urologic oncology for many years, his early
career path was winding and unpredictable.
In high school, he figured he would go into
engineering, psychology, or medicine. But
while attending Queens College at the City
University of New York, he became involved
in emergency medical services. He ended
up founding a volunteer ambulance unit in
New York City and decided to focus on emer-
gency medicine. Part of his focus evolved
into teaching cardiopulmonary resuscitation
(CPR) techniques to medical students. “It’s
hard to believe today, but when I was a medi-
cal student in the late 1970s, medical students
were not routinely learning CPR,” he said.

“Then I had a revelation as a third-year
medical student. When you’re in emergency
medicine, you spend a lot of time calling
trauma surgeons to come to the emergency
[department] and care for patients,” Gomella
said. “Seeing these trauma surgeons in action
first hand greatly impressed me. That is when
I decided I wanted to be a surgeon.”

After 2 years of general surgery, he
migrated to urology. He joked that he made the
move because he discovered that a doctor is
more likely to remain married after a urology
residency than a general surgery residency.
But in actuality, he was recruited by the chief
of urology, J. William McRoberts, MD, at his
training site, the University of Kentucky
College of Medicine, which made him realize
a urology residency could point him toward
research and a career in academic medicine.

Gomella completed a fellowship in surgical
oncology in the surgery branch at the National
Cancer Institute, where he worked with 2013
Giants of Cancer Care® award winner Steven
A. Rosenberg, MD, PhD, and urologic oncolo-
gist W. Marston Linehan, MD. In 1988, he was
recruited by former dean Joseph Gonnella, MD,
to help start a new cancer center at Jefferson
and has been there ever since.

“The grass is always greener someplace
else, but Jefferson and the Sidney Kimmel
Cancer Center have been a great place for me.
Many of my colleagues who got their start
here have gone on to greatness elsewhere,
but there are also a lot of my colleagues who
are still here fighting the good fight with us,”
Gomella said.

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Atezolizumab/Bevacizumab Combo Maintains Survival Advantage in Advanced HCC

by CAROLINE SEYMOUR

THE COMBINATION OF ATEZOLIZUMAB (Tecentriq) and bevacizumab (Avastin) continued to display improved survival compared with sorafenib (Nexavar) in previously untreated patients with advanced hepatocellular carcinoma (HCC), according to updated findings from the phase 3 IMbrave150 trial (NCT03434379) presented during the 2021 Gastrointestinal Cancers Symposium, presented by the American Society of Clinical Oncology.

At a median follow-up of 15.6 months, the median overall survival (OS) was 19.2 months (95% CI, 17.0-23.7) with the combination versus 13.4 months (95% CI, 11.4-16.9) with sorafenib (HR, 0.66; 95% CI, 0.52-0.85; \( P = .0009 \)). The median progression-free survival (PFS) was 6.9 months (95% CI, 5.7-8.6) versus 4.3 months (95% CI, 4.0-5.6), respectively (HR, 0.65; 95% CI, 0.53-0.81; \( P = .0001 \)).

"This is the longest [overall] survival seen in a phase 3 study of advanced liver cancer," lead study author, Richard S. Finn, MD, professor of clinical medicine, Department of Medicine, Division of Hematology/Oncology, at the David Geffen School of Medicine at UCLA, and director of the Signal Transduction and Therapeutics Program at the UCLA Jonsson Comprehensive Cancer Center, said in a virtual presentation of the data.

In May 2020, the FDA approved the combination for patients with unresectable or metastatic HCC who have not received prior systemic therapy. The approval was based on findings from the primary analysis of the IMbrave150 study in which both coprimary end points of PFS (HR, 0.59) and OS (HR, 0.58) were met.

The global, multicenter, randomized, open-label study enrolled 501 treatment-naïve patients with locally advanced or metastatic and/or unresectable HCC. Eligible patients were randomized 2:1 to 1200 mg of intravenous atezolizumab every 3 weeks plus 15 mg/kg of intravenous bevacizumab every 3 weeks (n = 336) or 400 mg of sorafenib twice daily (n = 165) until unacceptable toxicity or loss of clinical benefit.

Eligible patients had 1 or more measurable untreated lesions per RECIST 1.1 criteria, Child-Pugh class A liver function, and an ECOG performance status of 0 or 1. Updated patient disposition indicated that 40% of patients in the combination arm remained on study versus 26% in the sorafenib arm; 18% and 3% of patients remained on treatment, respectively. Sixty percent of patients in the combination arm discontinued the study compared with 74% in the sorafenib arm, primarily because of death (53% and 60%, respectively).

"The baseline characteristics have not changed from the primary analysis. The majority of patients came from outside of Asia and had high-risk features, such as an elevated \( \alpha \)-fetoprotein, macrovascular invasion, or extrahepatic spread," Finn said.

With an additional 12 months of follow-up, the updated results also demonstrated an 18-month OS rate of 52% with the combination versus 40% with sorafenib. The 18-month PFS rates were 24% and 12%, respectively.

"We see with longer follow-up that we have more responses with atezolizumab/bevacizumab than initially reported," Finn said.

The confirmed objective response rate by RECIST v1.1 criteria was 30% with the combination versus 11% with sorafenib, with complete response rates of 8% and less
Addition of FGFR Inhibitor to Chemotherapy Improves Survival in Advanced Gastric/GEJ Cancer

by GINA MAURO

BEMARITUZUMAB COMBINED WITH mFOLFOX6 demonstrated a 56% reduction in the risk of disease progression or death compared with placebo and mFOLFOX6 as a frontline treatment in select patients with FGFR2b-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma, according to results of the phase 2 FIGHT study (NCT03694522) presented during the 2021 Gastrointestinal Cancers Symposium.1

“The FIGHT trial is the first study to evaluate targeting the overexpression of FGFR2b in any cancer, and is the first randomized data set of any FGFR inhibitor in any malignancy,” lead study author Zev A. Wainberg, MD, codirector of UCLA Gastrointestinal Oncology Program, director of the Early Phase Clinical Research Support at Jonsson Comprehensive Cancer Center, and associate professor of medicine at the David Geffen School of Medicine at UCLA, said in a virtual presentation during the meeting.

“Bemarituzumab, when added to mFOLFOX6 chemotherapy, led to clinically meaningful and statistically significant improvements in PFS, OS [overall survival], and ORR [objective response rate].”

Bemarituzumab is an IgG1 antibody that is specific for FGFR2b isoform; it blocks growth factor signaling and works through an antibody-dependent cellular cytotoxicity mechanism, Wainberg said. Prior single-agent activity with bemarituzumab in later-line FGFR2b-positive gastric cancer elicited an 18% ORR with no dose-limiting toxicities.2

For patients with FGFR2b overexpression via immunohistochemistry (IHC) 2+/3+ at 10% or more of the sample (n = 96), the median progression-free survival (PFS) was 14.1 months in the bemarituzumab arm and 7.3 months in the placebo arm, (HR, 0.44; 95% CI, 0.25-0.77). The 1-year PFS rates were 57.0% and 26.4% in the combination and placebo arms, respectively.

CONFERENCE HIGHLIGHTS

**TABLE.** Updated Response Data From IMbrave150

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Atezolizumab + bevacizumab (n = 326)</th>
<th>Sorafenib (n = 159)</th>
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<td>Confirmed ORR (95% CI)</td>
<td>30% (25%-35%)</td>
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<td>Median DOR (95% CI)b</td>
<td>18.1 (14.6-NE)</td>
<td>14.9 (4.9-17.0)</td>
</tr>
</tbody>
</table>

CR, complete response; DCR, disease-control rate; DOR, duration of response; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

*Only patients with measurable disease at baseline were included in analysis of ORR. Responses assessed by RECIST 1.1 criteria.

*Only confirmed responders were included in the analysis of DOR.

Table was comprised of patients included in the global study population and 56 additional Chinese patients enrolled in the Chinese extension cohort.

In terms of safety, all-grade treatment-related adverse effects (TRAEs) occurred in 86% of patients in the combination arm versus 95% of patients in the sorafenib arm. The rates of grade 3/4 TRAEs were 43% and 46%, respectively. Grade 5 TRAEs occurred in 2% of patients in the combination arm versus less than 1% in the sorafenib arm.

AEs leading to withdrawal from any component of treatment occurred in 22% of patients in the combination arm compared with 12% in the sorafenib arm. AEs leading to dose interruption of any study treatment occurred in 59% and 44% of patients, respectively.

“The safety and tolerability of the combination remains consistent with what we saw in the primary analysis,” Finn concluded.

REFERENCE

In patients with FGFR2b overexpression via IHC 2+/3+ in at least 5% of the sample (n = 118), the median PFS was 10.2 months in the bemarituzumab arm versus 7.3 months with the placebo arm (HR, 0.54; 95% CI, 0.33-0.87). The 1-year PFS rates were 56.3% and 28.6%, respectively.

In the intention-to-treat (ITT) population (n = 155), the median PFS was 9.5 months and 7.4 months for the combination and placebo arms, respectively (HR, 0.68; 95% CI, 0.44-1.04; P = .0727). The 1-year PFS rates were 52.5% and 33.8%, respectively.

In the double-blind, placebo-controlled, phase 2 FIGHT trial, patients with unresectable locally advanced or metastatic gastric/GEJ adenocarcinoma were randomized 1:1 to receive bemarituzumab with a modified regimen of fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6; n = 77) or placebo/mFOLFOX6 (n = 76) every 2 weeks. The primary end point was investigator-assessed PFS; secondary end points included OS and ORR.

To be eligible for enrollment, patients could not have received prior therapy, had RECIST v1.1 evaluable disease, harbored FGFR2b overexpression by IHC and/or FGFR2 amplification by circulating tumor DNA (ctDNA), had an ECOG performance status of 0 or 1, and harbor HER2 positivity.

Initially, the trial was designed as a registration phase 3 trial with a planned 548 patients; however, the design was amended after enrolling 155 patients to a proof-of-concept phase 2 study with prespecified statistical assumptions.

Baseline demographics were similar between the 2 arms; overall, the median age was 59.7 years, more than half of patients were male. Further, approximately half in each arm were Asian. Patients were from the United States/European Union (42.6%), China (17.4%), or other countries in Asia (40.0%). In the bemarituzumab arm, 94.8% and 15.6% of patients had FGFR2b overexpression and amplification, respectively, compared with 97.4% and 17.9% in the placebo arm. Additionally, 83.2% of patients were IHC positive and ctDNA negative; 12.9% of patients were IHC positive and ctDNA positive, and 3.9% of patients were IHC negative and ctDNA positive.

Additionally, in the ITT population, data showed that the median OS was not reached in the bemarituzumab arm versus 12.9 months in the placebo arm (HR, 0.58; 95% CI, 0.35-0.95; P = .0268). The 1-year OS rates were 65.3% and 56.9%, respectively.

Similar to the PFS trends, the OS benefit with bemarituzumab increased with higher levels of FGFR2b overexpression. In the IHC 2+/3+ in at least 5% of the sample, the median OS was not reached with bemarituzumab versus 12.5 months with the placebo arm (HR, 0.52; 95% CI, 0.30-0.91). The 1-year OS rates were 67.9% and 55.5%, respectively.

In the IHC 2+/3+ in at least 10% of the sample, the median OS was not reached compared with 11.1 months with bemarituzumab and the placebo arms, respectively (HR, 0.41; 95% CI, 0.22-0.79).

The ORR in the ITT population was 47% with the combination and 33% with placebo/mFOLFOX6. For patients who had measurable disease at baseline, the ORRs were 53% and 40%, respectively, with a best change in tumor size at –41.7% and –29.9%, respectively. The median time to response was 1.84 months with bemarituzumab and 1.67 months with placebo/mFOLFOX6, and the median duration of response was 12.2 months and 7.1 months, respectively.

Regarding safety, grade 3 or higher adverse events (AEs) were observed in 82.9% of patients on bemarituzumab versus 74.0% of those on the placebo/mFOLFOX6 arm; the 2 most prominent increases in grade 3 or higher AEs with bemarituzumab included stomatitis (9.2% vs 1.3% with placebo) and dry eye (2.6% vs 0%, respectively). Grade 5 AEs occurred in 5 and 4 patients, respectively. Serious AEs occurred in 31.6% of patients treated with bemarituzumab and in 36.4% of patients on the placebo arm. AEs that led to mFOLFOX6 discontinuation occurred in 46.1% and 36.4% of patients on bemarituzumab/mFOLFOX6 and placebo/mFOLFOX6, respectively; these rates were 34.2% and 5.2% for bemarituzumab and placebo discontinuation, respectively. The duration of exposure to mFOLFOX6 was similar across the bemarituzumab (29.80 weeks) and placebo arms (26.47 weeks).

Corneal-related toxicities tend to be associated with FGFR inhibitors, Wainberg explained. All-grade and grade 3 or higher corneal-related AEs occurred in 67.1% and 23.7% of patients treated with bemarituzumab versus 10.4% and 0% of those on placebo/mFOLFOX6, respectively. The mean time to onset of, any grade, was 16.1 weeks on bemarituzumab/mFOLFOX6 and 11.6 weeks on placebo. Twenty patients discontinued bemarituzumab treatment due to corneal AEs, and 12 AEs did resolve with a median time to resolution of 27.0 weeks.

“The FIGHT trial results support a prospective randomized phase 3 study in gastric/gastroesophageal adenocarcinoma, and the evaluation of bemarituzumab in other FGFR2b-positive tumor types,” Wainberg concluded.

REFERENCES
Anlotinib Boosts OS in RAS/BRAF Wild-Type mCRC

DATA FROM THE PHASE 3 ALTER0703 trial (NCT02332499) demonstrated that anlotinib (AL3818), a multitargeted kinase inhibitor, significantly improved progression-free survival (PFS) and had a manageable safety profile in Chinese patients with refractory metastatic colorectal cancer (mCRC). Findings were presented at the 2021 Gastrointestinal Cancers Symposium.

In the mCRC treatment paradigm, antiangiogenic therapy is considered to be a standard-of-care in the first line; however, few options exist for patients who progress. Preliminary phase 2 data from a cohort of 31 patients suggested that anlotinib monotherapy may be an appropriate option, according to investigator Yihebali Chi, MD, PhD, of the Cancer Hospital at the Chinese Academy of Medical Sciences and Peking Union Medical College in Beijing.

In the earlier study, the agent showed an objective response rate (ORR) of 6.45% (95% CI, 0.8%-21.4%), all partial responses (PRs), and stable disease (SD) in 83.87% for a disease control rate (DCR) of 90.32% (95% CI, 74.2%-98.0%). The survival data for this early research showed a median PFS of 5.62 months (95% CI, 3.80-7.32) and a median overall survival (OS) of 9.33 months (95% CI, 8.46-10.21).

To further explore the antitumor efficacy of anlotinib as well as the safety of the agent, the phase 3 ALTER0703 study investigators evaluated anlotinib in the third-line setting and beyond for patients with mCRC who received 2 or more prior lines of chemotherapy (FIGURE).

In a 2:1 randomization, 282 patients in the study were given anlotinib 12 mg daily every 3 weeks in combination with best supportive care (BSC). Another 137 patients were given a matching placebo in combination with BSC. Treatment was continued until disease progression or intolerable toxicity.

Assessment of the primary end point showed that the median OS did not meet the requirements for significance. However, treatment with anlotinib yielded a longer median OS of 8.57 months (95% CI, 7.82-9.72) versus 7.16 months (95% CI, 6.24-8.80) in the placebo arm (HR, 1.02; 95% CI, 0.82-1.27; P = .87). A subgroup analysis of OS revealed an OS benefit with anlotinib among patients with RAS/BRAF wild-type disease. The median OS observed with anlotinib in this subgroup was 11.0 months (95% CI, 8.6-14.1) compared with 6.7 months (95% CI, 3.5-11.1) among patients given placebo (HR, 0.68; 95% CI, 0.47-0.99; P = .0005).

Secondary end point survival assessment showed a median PFS of 4.14 months (95% CI, 3.38-4.50) in the anlotinib arm versus 1.45 months (95% CI, 1.41-1.51) in the placebo arm (HR, 0.34; 95% CI, 0.27-0.43; P < .0001).

In terms of response, anlotinib led to an ORR of 4.26% (95% CI, 2.2%-7.3%), all PRs, SD in 52.5% of patients versus 19.7%, and progressive disease (PD) in 35.8% of those given placebo. Treatment-related AEs occurred in 97.5% of the anlotinib population compared with 86.1% of the placebo population, and these treatment-related AEs were grade 3 or higher in 66.7% of patients who received anlotinib versus 35.8% of those given placebo.

Hypertension was the most common AE observed. Pneumothorax was the most common serious treatment-related AE, which occurred in 4 patients.

Compared with the anlotinib arm, the DCR control rate among patients who received placebo was 30.7% (95% CI, 23.1%-39.1%) showing a significant difference (OR, 0.140; 95% CI, 0.089-0.221; P < .0001).

None of the adverse events (AEs) observed in the study were unexpected, according to investigators. AEs occurred in 99.7% of the anlotinib arm and 95.6% of the placebo arm. In addition, grade 3 or higher AEs occurred in 66.7% of patients who received anlotinib versus 35.8% of those given placebo. Treatment-related AEs occurred in 97.5% of the anlotinib population compared with 86.1% of the placebo population, and these treatment-related AEs were grade 3 or higher in 52.5% of patients versus 19.7%, respectively. Also, serious treatment-related AEs occurred in 12.4% of the anlotinib arm versus 7.3% of the placebo arm.

Hypertension was the most common AE observed. Pneumothorax was the most common serious treatment-related AE, which occurred in 4 patients.

REFERENCE
Ivosidenib Induces OS Benefit in IDH1+ Cholangiocarcinoma

by GINA MAURO

TAKING IVOSIDENIB (TIBSOVO) TABLETS led to a 21% reduction in the risk of death compared with placebo in previously treated patients with IDH1-mutant cholangiocarcinoma, according to the final overall survival (OS) analysis of the phase 3 ClarIDHy trial (NCT02989857), presented during the 2021 Gastrointestinal Cancers Symposium.1

Trial results showed that the median OS was 10.3 months in patients who received ivosidenib compared with 7.5 months for those who received placebo (HR, 0.79; 95% CI, 0.56-1.12; 1-sided P = .093). The 6-month OS rates were 69% and 57%, respectively. The 1-year OS rates were 43% and 36% for ivosidenib and placebo, respectively. Neither end point was adjusted for crossover.

As of May 31, 2020, 43 patients (70.5%) treated with placebo crossed over to the open-label ivosidenib arm upon radiographic disease progression. Results of a prespecified analysis to adjust for crossover to ivosidenib, based on a rank-preserving structural failure time model, showed that the median OS for patients in the placebo arm was 5.1 months (HR, 0.49; 95% CI 0.34-0.70, 1-sided P < .0001).

Based on these data, Agios Pharmaceuticals Inc, the developer of ivosidenib, plans to submit a supplemental new drug application for use of ivosidenib in this setting in the first quarter of 2021.2

“The ClarIDHy study represents the first phase 3 study of a targeted, oral therapeutic with a noncytotoxic mechanism of action in advanced IDH1-mutant cholangiocarci-

noma,” lead study author Andrew X. Zhu, MD, PhD, director of Liver Cancer Research at Massachusetts General Hospital and professor of medicine at Harvard Medical School in Boston, said in a presentation during the meeting. “Along with a tolerable safety profile and supportive quality of life, these final efficacy results demonstrate the clinical benefit of ivosidenib in this patient population, for which there is an urgent need for new therapies.” Zhu also serves as director of the Jiahui International Hospital Clinical Research both in Shanghai, China.

IDH1 mutations are found in an estimated 20% of intrahepatic cholangiocarcinoma cases. Although current therapeutics for localized disease include surgery, radiation, and/or other ablative treatments, no FDA-approved systemic treatments are available for patients with IDH1-mutated disease, and gemcitabine-based regimens are often used in those patients with newly diagnosed or advanced disease.

Ivosidenib is a first-in-class, oral small molecule IDH1 inhibitor. In May 2019, the FDA approved ivosidenib for the treatment of patients with IDH1-mutant acute myeloid leukemia (AML), specifically for those with newly diagnosed disease who are at least 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy. It also is approved for the treatment of patients with relapsed/refractory AML.3

In the international, randomized ClarIDHy study, 187 previously treated patients with IDH1-mutant cholangiocarcinoma were randomized 2:1 to receive oral ivosidenib at 500 mg daily (n = 126) or placebo (n = 61). Crossover from the placebo arm to ivosidenib was permitted following signs of radiographic progression.

Prior ClarIDHy data showed that ivosidenib led to a 63% reduction in the risk of disease progression or death versus placebo in previously treated patients with IDH1-mutant advanced cholangiocarcinoma.4 The median PFS was 2.7 months versus 1.4 months for ivosidenib and placebo, respectively (HR, 0.37; 95% CI, 0.25-0.54; 1-sided P < .0001). Six- and 12-month PFS rates were 32% and 22% with ivosidenib; no patients on placebo were progression free at either of these time points. Moreover, the disease control rates were 53% and 28%, respectively.

The median OS at the time of publication was 10.8 months with ivosidenib and 9.7 months for placebo (HR, 0.69; 95% CI, 0.44-1.10; P = .06). At 6 months, 67% of patients in the ivosidenib arm were alive; 59% on placebo were alive. At 1 year, the OS rate was 48% with ivosidenib and 38% for placebo.

With the longer follow-up, in which the data cutoff was May 31, 2020, investigators reported that 70.5% of patients who crossed over to receive ivosidenib. Eighteen patients on placebo did not cross over because of death (n = 12) or withdrawal of consent (n = 2), were on placebo but never dosed (n = 2), took the incorrect drug (n = 1), or received another therapy (n = 1). Disease progression was the most common reason for treatment discontinuation in both the ivosidenib (74.8%) and placebo arms (86.4%). Nineteen percent and 14.8% of patients on ivosidenib and placebo, respectively, remain on study.

The median duration of treatment of patients on ivosidenib was 2.8 months versus 1.6 months for those on placebo; patients who crossed over to receive ivosidenib had a median treatment duration of 2.7 months. Twenty-five patients (15.1%) remained on ivosidenib treatment for at least 1 year; this includes 6 patients who crossed over from the placebo group.

Regarding safety, updated results showed that the most common treatment-emergent adverse effects (AEs) in the total ivosidenib and placebo groups, respectively, were nausea (38.0% vs 28.8%), diarrhea (33.1% vs 16.9%), fatigue (28.9% vs 16.9%), abdominal pain (22.3% vs 15.3%), cough (21.7% vs 8.5%), decreased appetite (21.7% vs 18.6%), ascites (19.9% vs 15.3%), and vomiting (19.9% vs 18.6%).

Grade 3 or higher treatment-emergent AEs (TEAEs) were seen in 53% of ivosidenib-treated patients, which includes those who also crossed over from placebo, compared with 37.3% for placebo-treated patients. The most common grade 3 or higher TEAEs reported in the ivosidenib and placebo groups, respectively, were ascites (9.0% vs 6.8%, respectively), blood bilirubin increase (5.4% vs 1.7%), and anemia (7.2% vs 0%).

For a full list of references, see the article at https://bit.ly/2Ytf44V.
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T-CELL THERAPY

Investigators Aim Novel T-Cell Therapy at Solid Tumor Target

by DENISE MYSHKO

ADP-A2M4CD8, A NOVEL T-cell therapy, is being investigated in a range of tumor types that express MAGEA4, an antigen expressed in solid tumors that investigators say represents a promising target for cellular immunotherapy.

The ongoing phase 1 SURPASS trial (NCT04044859), a first-in-human study, is open to patients with 8 cancer types, although investigators are focused on recruiting participants with gastrointestinal cancers, head and neck squamous cell carcinoma (HNSCC), and lung and bladder cancers.

Based on early positive data, investigators are planning a phase 2 trial in patients with gastrointestinal cancers.1

ADP-A2M4CD8 is an autologous therapy directed toward the HLA complex/MAGEA4 antigen. The therapy is manufactured from the patient’s peripheral blood cells, which are harvested through leukapheresis and transduced with a lentiviral vector containing a MAGEA4 T-cell receptor (TCR) and expanded. Specific peptide-enhanced affinity receptor (SPEAR) technology is used to selectively engineer TCRs modified to enhance binding to cancer cells.1,2

“The SPEAR T-cells are an interesting technology,” David S. Hong, MD, the lead investigator in the SURPASS trial, said in an interview with OncologyLive®. “The SPEAR T-cells are CD4 and CD8α cells that have been reengineered to express a TCR that can bind to these HLA-restricted receptor and antigen complexes on cancer cells.”

MAGEA4, a cancer testis antigen, is broadly expressed in many solid tumor types.

In a study of 585 samples in 21 tumor types, investigators found that MAGEA4 was expressed in 36.6% of samples (range, 30.7%-37.3%). The antigen was identified in 9 tumor types, including 54.9% of esophageal cancers, 37.5% of HNSCCs, and 35.0% of gastric cancers.3

Investigators are seeking a solid tumor target for T-cell therapies, said Hong, who is deputy chair of the Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center in Houston.

So far, chimeric antigen receptor (CAR) T-cell therapies that bind to CD19 have succeeded in hematologic malignancies, with 4 FDA-approved products. “Thus far, we haven’t seen strong responses in treating solid tumors with available cellular therapies, in large part because antigens expressed are not restricted to the tumors,” Hong said in a news release.4

ADP-A2M4CD8 represents another step in the development of the MAGEA4-targeting T-cell therapy. A previous version, called ADP-A2M4, showed activity in synovial sarcoma, Hong said, but investigators sought to improve its efficacy by adding SPEAR T cells that coexpress the CD8α receptor. “There was still a way to go with other tumor types, such as esophageal and head and neck and other cancers. Adding the CD8α coreceptors to the existing construct allows for greater cytotoxicity and enhances engagement across the wider immune system,” he said.

THE SURPASS TRIAL

In the SURPASS trial, investigators are seeking to recruit 30 patients. Although the focus is on gastrointestinal cancers, HNSCC, and lung and bladder cancers, enrollment also is open for patients with ovarian, melanoma, myxoid/round cell liposarcoma (MRCLS), or synovial sarcoma. Enrollment had been paused for several months because of the coronavirus disease 2019 (COVID-19) pandemic, but is now ongoing, Hong said.

“This is an in-patient trial, and the hospitals not only at MD Anderson but everywhere were worried they were going to get overwhelmed with COVID patients in the ICUs,” Hong said.

To be eligible for the trial, patients must have MAGEA4 expression of at least 2+

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**Eligibility criteria**

- Diagnosis of advanced gastrointestinal cancer, HNSCC, NSCLC, ovarian cancer, urothelial carcinoma, synovial sarcoma, MRCLS, or melanoma
- Positive for at least 1 HLA-A*02 inclusion allele
- Measurable disease according to RECIST v1.1
- MAGEA4 ≥ 2+ on IHC staining
- ECOG score of 0 or 1
- LVEF ≥ 50% or the institutional lower limit of normal range, whichever is lower
- No prior treatment with investigational cancer therapy within 21 days
- Not pregnant or breastfeeding
- Signed informed consent

**End points**

- BOR, best overall response; DOR, duration of response; DOSD, duration of stable disease; ECOG, Eastern Cooperative Oncology Group; IMMHC, immunohistochemistry; HNSCC, head and neck squamous cell carcinoma; IHC, immunohistochemistry; LVEF, left ventricular ejection fraction; MRCLS, myxoid/round cell liposarcoma; NSCLC, non–small-cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression free survival; TRAE, treatment-related adverse events; TTR, time to response.

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**FIGURE. ADP-A2M4CD8 T-Cell Therapy in Solid Tumors**

**SURPASS Phase 1 Trial**

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>3-6 patients ADP-A2M4CD8 doses 1 × 10⁹ (range, 0.8–1.2 × 10⁹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 2</td>
<td>3-6 patients ADP-A2M4CD8 doses 5 × 10⁹ (range, 1.2–6 × 10⁹)</td>
</tr>
</tbody>
</table>

**Expansion cohort**

Up to 30 patients ADP-A2M4CD8 doses 1.2–10 × 10⁹ (includes dose escalation)
in 30% or more of tumor cells on immunohistochemistry staining and test positive for at least 1 HLA-A*02 inclusion allele. Participants also must have received or refused standard antitumor regimens with no more than 3 lines of prior systemic therapy in the metastatic or unresectable locally advanced setting. The study uses a modified 3+3 design, with up to 2 dose cohorts plus an expansion cohort (FIGURE). After enrollment, patients undergo leukopheresis, and their white blood cells are sent to Adaptimmune Therapeutics, the developer of ADP-A2M4CD8, for engineering with SPEAR T cells. Four to 7 days before infusion, patients undergo lymphodepletion comprised of fludarabine at 30 mg/m² daily for 4 days and cyclophosphamide at 600 mg/m² daily for 3 days.

After receiving the ADP-A2M4CD8 therapy, patients remain in the hospital for a minimum of 3 days and are discharged at the investigator’s discretion. Investigators will monitor patients during disease progression, withdrawal from the interventional phase of study, or death to assess for efficacy and safety. In the first year after infusion, investigations monitor and assess patients at months 3, 6, and 12. From years 2 to 5, investigators monitor patients every 6 months. After year 5, investigators assess patients annually for up to 15 years.

This is a complex trial to administer, Hong said. “We have to determine the timing for the leukopheresis and the timing for the dose-escalation trial, as well as the timing for the lymphodepletion. We have to determine insurance clearance, etc,” he said.

The trial is being conducted in 17 sites in the United States, Canada, and Spain.

**INITIAL FINDINGS FROM SURPASS**

Hong and colleagues presented data during the Society for Immunotherapy of Cancer’s annual meeting in November 2020 demonstrating early efficacy signals and a manageable safety profile for ADP-A2M4CD8. Among 6 patients with heavily pretreated advanced cancers, 3 were treated with target doses of 1 billion SPEAR T cells and 3 received target doses of 5 billion SPEAR T cells. Initial responses appear promising and have the potential to offer long-term benefit for patients in this space, Hong said. Notably, 5 out of 6 patients experienced initial tumor shrinkage following T-cell infusion. There were 2 confirmed partial responses (PRs)—in 1 patient with esophageal cancer, for any-grade AEs, 4 patients experienced cytokine release syndrome (CRS) and 3 had fatigue. “What’s interesting is that we don’t see the level and the percentage of cytokine release syndrome that you would see with CAR T therapy,” Hong said. “The most common adverse effects have been associated with the lymphodepletion, such as neutropenia or lymphopenia. The vast majority of these patients had mild symptoms of CRS. Some had mild fever. Some had some mild fatigue.”

Preclinical data presented at the 2019 American Association for Cancer Research annual meeting found that ADP-A2M4CD8 increased T-cell activation and improved engagement with the immune system in dendritic cells and T-cells cocultured with MAGEA4–positive cancer cell lines. There was no additional off-target reaction in vitro. This was a proof-of-concept study that focused on CD4+ T-cell function using in vitro assays.

Adaptimmune plans to launch SURPASS-2, a phase 2 trial of ADP-A2M4CD8 in gastroesophageal cancers, during the first half of 2021. The company expects to file a biologics license application for ADP-A2M4CD8 in gastroesophageal cancers in 2024.

Meanwhile, investigators continue to evaluate ADP-A2M4 in the phase 2 SPEARHEAD 1 trial (NCT04044768) in patients with advanced synovial sarcoma or MRCLS. The registrational study is projected to complete enrollment in the first quarter of 2021.

Additionally, ADP-A2M4 is being studied in combination with pembrolizumab (Keytruda) in a pilot phase 2 trial, SPEARHEAD 2 trial (NCT04408898), in patients with recurrent or metastatic head and neck cancer.

Updated findings from a phase 1 trial of ADP-A2M4 in patients with synovial sarcoma who are MAGE-A4 positive found that 7 of 16 patients (44%) had confirmed PRs per RECIST criteria, with disease control in 15 patients (94%). There was a median duration of response of 28 weeks (range, 12-72+), with 2 PRs that were ongoing beyond 72 weeks; and 11 of the 16 patients were alive at the time of data cutoff on September 1, 2020.

**REFERENCES**

When treating non-metastatic castration-resistant prostate cancer (nmCRPC), survival is just the half of it.

**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

40 MONTHS

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

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

NUBEQA®—Focus on both MFS and tolerability

PROVEN TOLERABILITY

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

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

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

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

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

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

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

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

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=354). All patients received concurrent ADT (treatment with GnRH analog or previous bilateral orchiectomy). The primary endpoint was MFS, defined as the time from randomization to the time of first evidence of BCRP-confirmed distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, †18F bone scan by BCRP, unacceptable toxicity, or withdrawal.

†All-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 same lab abnormalities were, respectively, 4% vs 0.6%, 0.5% vs 0.2%, and 0.1% vs 0%.

NUBEQA Free Trial Program

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.

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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.

Start new patients with up to 2 months free.*

Visit NUBEQAhcp.com

Please see the following pages for brief summary of full Prescribing Information.
NUBEQA® (darolutamide) tablets, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NUBEQA is indicated for the treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

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

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

6 ADVERSE REACTIONS

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

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

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

Permanent discontinuation due to adverse reactions occurred in 9% of patients receiving NUBEQA or placebo. The most frequent adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%).

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

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

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

Table 1: Adverse Reactions in ARAMIS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NUBEQA (n=554)</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</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

1 Includes fatigue and asthenia

2 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

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

Table 2: Laboratory Test Abnormalities in ARAMIS

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>NUBEQA (n=554)</th>
<th>Placebo (n=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades2</td>
<td>Grade 3-42</td>
</tr>
<tr>
<td>Neutrophil count decrease</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>AST increased</td>
<td>23</td>
<td>0.5</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>16</td>
<td>0.1</td>
</tr>
</tbody>
</table>

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

2 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on NUBEQA

Combined P-gp and Strong or Moderate CYP3A4 Inducer

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.

Combined P-gp and Strong CYP3A4 Inhibitors

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure [see Clinical Pharmacology (12.3)] which may increase the risk of BCRP substrate-related toxicities.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy [see Clinical Pharmacology (12.1)]. Animal embryo-fetal developmental toxicity studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Contraception

Males

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

Infertility

Males

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

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

Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to systemic toxicity in patients with intact hepatic and renal function [see Clinical Pharmacology (12.3)]. In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies to evaluate the carcinogenic potential of darolutamide have not been conducted.
Darolutamide was clastogenic in an in vitro chromosome aberration assay in human peripheral blood lymphocytes. Darolutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in the in vivo combined bone marrow micronucleus assay and the Comet assay in the liver and duodenum of the rat.
Fertility studies in animals have not been conducted with darolutamide. In repeat-dose toxicity studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), tubular dilatation of testes, 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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Manufactured for: Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981 USA
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ExteNET Data Shed Light on TKI Utility in HER2+ Breast Cancer

by JESSICA HERGERT

Outcomes in ExteNET Subgroups of Clinical Interest

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ITT population</th>
<th>Hormone receptor–positive/≤ 1 year*</th>
<th>Hormone receptor–positive/≤ 1 year* with no pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neratinib (n = 1420)</td>
<td>Placebo (n = 1420)</td>
<td>Neratinib (n = 670)</td>
</tr>
<tr>
<td>CNS events</td>
<td>16</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Cumulative incidence of CNS recurrences (95% CI)</td>
<td>(1.3) (0.8%-2.1%)</td>
<td>(1.8) (1.2%-2.7%)</td>
<td>(0.7) (0.2%-1.7%)</td>
</tr>
<tr>
<td>Estimated 8-year OS rate</td>
<td>90.1%</td>
<td>90.2%</td>
<td>91.5%</td>
</tr>
</tbody>
</table>

CNS, central nervous system; ITT, intention-to-treat; OS, overall survival; pCR, pathologic complete response.
*Patients with hormone receptor–positive breast cancer who initiated treatment within 1 year of completing prior trastuzumab-based therapy.

Ultimately, these findings raise other questions regarding the utility of other HER2-directed tyrosine kinase inhibitors (TKIs) such as tucatinib (Tukysa), which has the potential to make its way into the early-stage setting, explained Brufsky. “TKIs [have some efficacy] in the brain and [are potentially] stopping the progression of brain metastases,” he said. “It makes perfect sense [that neratinib would have efficacy in the early-stage setting].”

Moreover, as our understanding of TKIs continues to evolve, developing a predictive biomarker to inform clinicians which patients are likely to develop brain metastases could fill a significant unmet need in the field.

“[Currently], we don’t know, clinically or pathologically, who gets brain metastases,” said Brufsky, who is a professor of medicine and the associate chief in the Division of Hematology/Oncology at the University of Pittsburgh School of Medicine. “Some of us who have seen a lot of patients have a hint, but there is nothing in the literature that says a patient with this presentation of HER2-positive early-stage breast cancer is going to develop brain metastases. It would be nice to have some way of figuring that out.”

In an interview with OncologyLive®, Brufsky, who is also the medical director of Magee-Womens Cancer Program, codirector of the Comprehensive Breast Cancer Center, and associate director of Clinical Investigation at the University of Pittsburgh Medical Center Hillman Cancer Center, discussed the updated findings from the ExteNET trial. He also talked about the role of TKIs in treating patients with brain metastases and the unanswered questions that future research efforts should aim to address.

What notable findings were presented from the updated ExteNET analysis?

The key findings of ExteNET are that the invasive disease-free survival (iDFS) benefit is maintained. [Also] an OS benefit was seen in the subgroups that are most relevant to us today. Most women with HER2-positive early-stage breast cancer will get neoadjuvant therapy with pertuzumab [Perjeta], trastuzumab, and some sort of chemotherapy combination. If patients have residual disease, they get T-DM1 [ado-trastuzumab emtansine; Kadcyla] for 17 doses.

The issue is that these patients are at a higher risk of recurrence. What do you do? [Data from] the ExteNET trial showed that a prespecified subgroup of patients who get 1 year of neratinib post trastuzumab have a 7% to 8% iDFS benefit and a 7% OS benefit, with the caveat that patients were not treated with neoadjuvant T-DM1. These are patients who are really at the highest risk of recurrence. [The ExteNET data were] pretty strong,
Would you offer neratinib to most patients with early-stage HER2-positive breast cancer?

No, but I would take certain patients with a lot of lymph nodes involved, a large tumor, or a lot of residual disease. I would probably offer [neratinib] even after a year of T-DM1 even though that is not the study population. The reason for that was teased out in very preliminary data, with very small numbers in the ExteNET update. It appears that patients who got neratinib had fewer brain metastases. When we go back and look at [data from the] KATHERINE trial [NCT01772472], we see that there is an 11% distant-relapse rate, half of which are brain metastases. This means that the T-DM1 doesn’t get into the CNS. These are extraordinarily preliminary data.

On the other hand, if we look at metastatic breast cancer and the NEERTT trial [NCT00915018], which was paclitaxel and trastuzumab versus paclitaxel and neratinib, neratinib cut the incidence of brain metastases as first recurrence in half. [Neratinib] is doing something. Plus, we know from the HER2CLIMB trial [NCT02614794] that tucatinib is doing something in the metastatic setting.

There is a trial called CompassHER2 RD [NCT04457596], which is going to [evaluate] T-DM1 with or without tucatinib, that [will begin enrollment] in the not-too-distant future. That trial will help us answer the question [of whether tucatinib in this setting is an advantage]. But until we get those data, [neratinib] is something to consider because brain metastases are devastating in patients who [develop them] as the first site of recurrence even though they’ve done well systemically.

It is important for us to give that some thought, although, again, these are very preliminary data… People [are] talking about whether [the ExteNET investigators] extended themselves beyond what [data] were there, but on the other hand, these were all hypothesis-generating data. It’s very intriguing. To me, the survival benefit is clear because it was a prespecified [subset] and [the ExteNET data are] something we can use to justify [giving neratinib in the early-stage setting].

What is next for TKIs in this space?

There are a lot of nonrandomized trials in the metastatic setting of T-DM1 with or without neratinib. The concept of TKIs [has led to] the hope that one day we will have a genetic predictor or a clinical pathologic predictor of which patients are going to be more susceptible to brain metastases. We’ll be able to look at a patient’s primary tissue and focus our HER2[-directed] TKIs on those individuals. That is where all this is going, but again, that depends on getting a predictor, which is the hard part.

If tucatinib moves into the early-stage setting, will treatment decisions become more complex?

We always have these problems. We had them with aromatase inhibitors; we have them with CDK4/6 inhibitors now. Everything has a safety profile. The diarrhea with neratinib can be managed very successfully with dose escalation. We start with 120 mg or 160 mg per day of neratinib and gradually dose escalate over the first month. During that time, we are very liberal with antidiarrheals, such as loperamide [Entocort], budesonide [Entocort]. These are available and [Puma Biotechnology, Inc] provides [antidiarrheals] to patients for free when they get [neratinib].

Although the diarrhea can be controlled, there are people who just can’t tolerate [neratinib]. I have maybe 1 in 10 or 1 in 5 patients who just cannot tolerate it, and we have to stop [the drug]. However, the remainder of patients get through it and want to continue it.

[Overall], this is why tucatinib is a potential option because it has less [severe] diarrhea.

Is there anything else you would like to add regarding the future utility of TKIs in HER2-positive breast cancer?

The big problem in HER2-positive early-stage [and] metastatic breast cancer is that all of us are starting to come to the conclusion that we are doing a really good job of controlling systemic disease. However, [HER2-positive breast cancer] is just like pediatric leukemia, where 40 or 50 years ago we realized there were sanctuary sites [of cancer] that our therapies cannot get to. Now we have therapies like HER2[-directed] TKIs that can get into those sanctuary sites.

[It now becomes a matter] of which [drugs] do we use and how do we use them. If a patient is resistant to one TKI in the metastatic setting, do they respond to another? Does it depend on what kind of mutation the patient has, if they have any? Does it depend on [HER2] amplification? These are the sort of questions that investigators are going to be exploring in this field over the next couple of years.

REFERENCE


Brufsky on the Treatment Landscape for TNBC

For more from Adam M. Brufsky, MD, PhD, visit OncLive.com for an exclusive interview about the future role of chemotherapy in triple-negative breast cancer (TNBC).

According to Brufsky, chemotherapy will likely retain a role in the treatment of patients with TNBC for at least the next 5 to 10 years.

INDICATION
CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

SELECT IMPORTANT SAFETY INFORMATION
HEMORRHAGE
- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%. Grade 3-5 hemorrhage incidence ranged from 2-5%.
- Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in REGARD and RAINBOW; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown.
- Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

Please see Important Safety Information and Brief Summary of Prescribing Information for CYRAMZA on subsequent pages.
"I'm in this for as long as I can be."

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

Adding CYRAMZA to paclitaxel nearly doubles the response vs paclitaxel alone1,2

**ORR (Complete and Partial Response): Supportive Outcome Measure**

**RAINBOW ORR: percent of patients (95% CI)**

<table>
<thead>
<tr>
<th>CYRAMZA + paclitaxel (n=330)</th>
<th>Placebo + paclitaxel (n=335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28% (23, 33)</td>
<td>16% (13, 20)</td>
</tr>
</tbody>
</table>

**P>0.001**

- Disease progression and tumor response were assessed by investigators in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
- 2 complete response in CYRAMZA-treated patients and 1 complete response in the placebo-treated patients

**CYRAMZA plus paclitaxel significantly extended OS and PFS1**

**Overall Survival: Major Outcome Measure Median-Months (95% CI)**

<table>
<thead>
<tr>
<th>CYRAMZA + paclitaxel (n=330)</th>
<th>Placebo + paclitaxel (n=335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.6 MONTHS* (8.5, 10.8)</td>
<td>7.4 MONTHS* (6.3, 8.4)</td>
</tr>
</tbody>
</table>

**Hazard ratio=0.81 (0.68, 0.96); P=0.017**

- The percentage of deaths at the time of analysis was 78% [256 patients] and 78% [260 patients] in the CYRAMZA plus paclitaxel and placebo plus paclitaxel treatment arms, respectively

**PFS: Supportive Outcome Measure Median-Months (95% CI)**

<table>
<thead>
<tr>
<th>CYRAMZA + paclitaxel (n=330)</th>
<th>Placebo + paclitaxel (n=335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4 MONTHS* (4.2, 5.3)</td>
<td>2.9 MONTHS* (2.8, 3.0)</td>
</tr>
</tbody>
</table>

**Hazard ratio=0.64 (0.54, 0.75); P<0.001**

- The percentage of events at the time of analysis was 85% [279 patients] and 88% [296 patients] in the CYRAMZA plus paclitaxel and placebo plus paclitaxel treatment arms, respectively
- 56 of 279 events in CYRAMZA-treated patients and 55 of 296 events in placebo-treated patients were deaths

**STUDY DESIGN:** The phase III RAINBOW trial evaluated the efficacy and safety of CYRAMZA plus paclitaxel vs placebo plus paclitaxel in patients with locally advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- and platinum-containing chemotherapy. Major efficacy outcome measure was OS. Supportive efficacy outcome measures were PFS and ORR. All patients were ECOG PS 0 or 1. Prior to enrollment, 97% of patients had progressed during treatment or within 4 months after the last dose of first-line chemotherapy for metastatic disease. Twenty-five percent of patients had received anthracycline in combination with platinum/fluoropyrimidine therapy, while 75% did not. Patients were randomized 1:1 to CYRAMZA 8 mg/kg (n=330) or placebo (n=335) every 2 weeks (on days 1 and 15) of each 28-day cycle. Patients in both arms received paclitaxel 80 mg/m2 on days 1, 8, and 15 of each 28-day cycle.1,3

**SELECT IMPORTANT SAFETY INFORMATION**

**GASTROINTESTINAL PERFORATIONS**
- CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from <1-2%.
- Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

**IMPAIRED WOUND HEALING**
- CYRAMZA has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds.
- Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 2 weeks following a major surgical procedure and until adequate wound healing. The safety of resumption of CYRAMZA after resolution of wound healing complications has not been established.

Please see Important Safety Information on next page and Brief Summary of Prescribing Information for CYRAMZA on subsequent pages.
**IMPORTANT SAFETY INFORMATION FOR CYRAMZA® (ramucirumab)**

**Warnings and Precautions**

**Hemorrhage**
- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%. Grade 3-5 hemorrhage incidence ranged from 2-5%.
- Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in REGARD and RAINBOW; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown.
- Permanently discontinue CYRAMZA in patients who experience severe Grade 3 or 4 bleeding.

**Gastrointestinal Perforations**
- CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from <1-2%.
- Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

**Impaired Wound Healing**
- CYRAMZA has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds.
- Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 2 weeks following a major surgical procedure and until adequate wound healing. The safety of resumption of CYRAMZA after resolution of wound healing complications has not been established.

**Arterial Thromboembolic Events (ATEs)**
- Serious, sometimes fatal, ATEs, including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, occurred across clinical trials. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade ATE was 1-3%. Grade 3-5 ATE incidence was <1-2%.
- Permanently discontinue CYRAMZA in patients who experience an ATE.

**Hypertension**
- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA. In 1116 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension ranged from 11-26%. Grade 3-5 hypertension incidence ranged from 6-16%.
- Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Withhold CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

**Infusion-Related Reactions (IRR)**
- IRR, including severe and life-threatening IRR, occurred in CYRAMZA clinical trials. Symptoms of IRR included rigor/hypersensitivity, back pain/limb pain, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade ATE was 1-3%. Grade 3-5 ATE incidence was <1-2%.
- Permanently discontinue CYRAMZA in patients who experience an ATE.

**Warnings and Precautions**

**Proteinuria Including Nephrotic Syndrome**
- In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade proteinuria ranged from 3-34%. Grade ≥3 proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%.
- Monitor for proteinuria. Withhold CYRAMZA for urine protein levels that are 2 or more grams over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to less than 2 grams over 24 hours. Permanently discontinue CYRAMZA for urine protein levels greater than 3 grams over 24 hours or in the setting of nephrotic syndrome.

**Thyroid Dysfunction**
- In 2137 patients with various cancers treated with CYRAMZA, the incidence of Grade 1-2 hypothyroidism ranged from <1-3%; there were no reports of Grade 3-5 hypothyroidism. Monitor thyroid function during treatment with CYRAMZA.

**Embryo-Fetal Toxicity**
- CYRAMZA can cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for 3 months after the last dose.

**Lactation**
- Because of the potential risk for serious adverse reactions in breastfed children from ramucirumab, advise women not to breastfeed during treatment with CYRAMZA and for 2 months after the last dose.

**Adverse Reactions**

** REGARD:**
- The most common adverse reactions (All Grades) observed in single agent CYRAMZA-treated gastric cancer patients at a rate of ≥5% and ≥2% higher than placebo were hypertension (16% vs 8%), diarrhea (14% vs 7%), headache (9% vs 3%), and hyponatremia (6% vs 2%).
- The most common serious adverse reactions with CYRAMZA were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients in REGARD were: neutropenia (4.7%), epistaxis (4.7%), rash (4.2%), intestinal obstruction (2.1%), and arterial thromboembolic events (1.7%).
- Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including Grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and IRR. In REGARD, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria vs 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in REGARD was 0.8% and the rate of IRR was 0.4%.

**RAINBOW:**
- The most common adverse reactions (All Grades) observed in patients treated with CYRAMZA with paclitaxel at a rate of ≥5% and ≥2% higher than placebo with paclitaxel were fatigue/asthenia (57%/vs 44%), neutropenia (54%/vs 31%), diarrhea (32%/vs 23%), epistaxis (31%/vs 7%), hypertension (25%/vs 6%), peripheral edema (25%/ vs 14%), stomatitis (20%/vs 7%), proteinuria (17%/vs 6%), thrombocytopenia (13%/vs 6%), hyperalbuminemia (11%/vs 5%), and gastrointestinal hematologic events (10%/vs 6%).
- The most common serious adverse reactions with CYRAMZA with paclitaxel were neutropenia (3.7%) and febrile neutropenia (2.4%). 19% of patients who received CYRAMZA with paclitaxel received granulocyte colony-stimulating factors.
- Adverse reactions resulting in discontinuation of any component of the CYRAMZA with paclitaxel combination in ≥2% of patients in RAINBOW were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of patients receiving CYRAMZA with paclitaxel were sepsis (3.1%), including 5 fatal events, and gastrointestinal perforations (1.2%), including 1 fatal event.

Please see Brief Summary of Prescribing Information for CYRAMZA on next page.

RB-6 HCP ISI 29 MAY 2020

References:
Gastric Cancer

The safety of CYRAMZA was evaluated in REGARD and RAINBOW. Patients in both trials had locally advanced or metastatic gastric or gastro-esophageal junction (GE) adenocarcinoma with disease progression on or after fluoropyrimidine- or platinum-containing chemotherapy.

CONTRINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage

CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade 3 hemorrhagic events. Across six clinical studies in 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%. Grade 3-5 hemorrhage incidence ranged from 2-5%. Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in REGARD and RAINBOW; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. Permanently discontinue CYRAMZA in patients who experience severe Grade (3 or 4) bleeding.

Gastrointestinal Perforations

CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Across six clinical studies in 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from <1-2%. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF or VEGFR pathway. CYRAMZA, a VEGFR2 antagonist, has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds. Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 2 weeks following a major surgical procedure and until adequate wound healing. The safety of resumption of CYRAMZA after resolution of wound healing complications has not been established.

Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATEs), including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral infarction, occurred across clinical trials. Across six clinical studies in 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade ATE ranged from 1-3%. Grade 3-5 ATE incidence was <1-2%. Permanently discontinue CYRAMZA in patients who experience an ATE. Hypertension

An increased incidence of severe hypertension occurred in patients receiving CYRAMZA. Across five clinical studies, excluding REGARD, in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension ranged from 11-28%. Grade 3-5 hypertension incidence ranged from 6-15%. Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Withhold CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-related Reactions (IRR)

Infusion-related reactions (IRR), including severe and life-threatening IRR, occurred in CYRAMZA clinical trials. The majority of IRR across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRR included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospams, supraventricular tachycardia, and hypotension. Across six clinical studies in 2137 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR ranged from <1-9%. Grade 3-5 IRR incidence was <1%. Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3-4 IRR.

Worsening of Pre-existing Hepatic Impairment

Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration. Based on safety data from REGARD and RAINBOW, symptoms including bronchospams, supraventricular tachycardia, and hypotension, occurred across clinical trials. Across six clinical studies in 2137 patients with various cancers treated with CYRAMZA, in which premedication was recommended or required, the incidence of all Grade IRR ranged from <1-9%. Grade 3-5 IRR incidence was <1%. Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3-4 IRR.

Posterior Reversible Encephalopathy Syndrome

Posterior Reversible Encephalopathy Syndrome (PRES) (also known as Posterior Reversible Leukoencephalopathy Syndrome [PRES]) has been reported in ~0.1% of 2137 patients enrolled in six clinical studies with CYRAMZA. Symptoms of PRES include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension. Confirm the diagnosis of PRES with magnetic resonance imaging and permanently discontinue CYRAMZA in patients who develop PRES. Symptoms may resolve or improve within days, although some patients with PRES can experience ongoing neurologic sequelae or death.

Respiratory, Thoracic, and Mediastinal

Respiratory, thoracic, and mediastinal events have been reported, including bronchospasm, dyspnea, hypoxia, and wheezing. Across clinical trials, CYRAMZA administered as a single agent, clinically relevant adverse reactions (including Grade >3) related to the respiratory system occurred in 1-2% of patients receiving CYRAMZA. Across clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described in the Warnings and Precautions section reflect exposure to CYRAMZA in 2137 patients from six studies: REGARD, RAINBOW, RAISE, REVEL, REACH-2, and RELAY.

Table 1: Adverse Reactions Occurring in ≥5% of Patients with a ≥2% Difference Between Arms in REGARD

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CYRAMZA (N=236)</th>
<th>Placebo (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

* Hypertension is a consolidated term.

Clinically relevant adverse reactions reported in <1% and <5% of CYRAMZA-treated patients in REGARD were neutropenia (4.7%), epistaxis (4.7%), rash (4.2%), intestinal obstruction (2.1%), and arterial thromboembolic events (1.7%).

Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including Grade >3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and IRR. In REGARD, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria versus 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in REGARD was 0.6% and the rate of IRR was 0.4%.

Table 2: Adverse Reactions Occurring in ≥5% of Patients with a ≥2% Difference Between Arms in RAINBOW

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CYRAMZA + Paclitaxel (N=257)</th>
<th>Placebo + Paclitaxel (N=239)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/Asthema</td>
<td>57</td>
<td>12</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>54</td>
<td>41</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Slomatitis</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage eventsa</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Renal and Urinary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

* Neutropenia, gastrointestinal hemorrhage events, hypertension, proteinuria, and hypoalbuminemia are consolidated terms.

Includes 1 fatal event in the CYRAMZA arm.

Clinically relevant adverse reactions reported in <1% and <5% of patients receiving CYRAMZA with paclitaxel were sepsis (3.1%), including 5 fatal events, and gastrointestinal perforations (1.2%), including 1 fatal event.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CYRAMZA (N=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td></td>
</tr>
<tr>
<td>Grade 3 (%)</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Fatigue/Asthema</td>
<td>57</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>25</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>54</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
</tr>
<tr>
<td>Slomatitis</td>
<td>20</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage eventsa</td>
<td>10</td>
</tr>
</tbody>
</table>

* Neutropenia, gastrointestinal hemorrhage events, hypertension, proteinuria, and hypoalbuminemia are consolidated terms.

Includes 1 fatal event in the CYRAMZA arm.
Immunogenicity
As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to CYRAMZA with the incidences of antibodies to other products may be misleading.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of CYRAMZA. Because such reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
- Blood and lymphatic system: Thrombotic microangiopathy
- Neoplasms benign, malignant, and unspecified: Hemangioma
- Respiratory, thoracic, and mediastinal: Dysphonia
- Vascular: Arterial (including aortic) aneurysms, dissections, and rupture

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to a pregnant woman. There are no available data on CYRAMZA use in pregnant women. Animal models link angiogenesis, VEGF and VEGFR2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise a pregnant woman 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
No animal studies have been specifically conducted to evaluate the effect of ramucirumab on reproduction and fetal development. In mice, loss of the VEGFR2 gene resulted in embryo-fetal death and these fetuses lacked organized blood vessels and blood islands in the yolk sac. In other models, VEGFR2 signaling was associated with development and maintenance of endometrial and placental vascular function, successful blastocyst implantation, maternal and feto-placental vascular differentiation, and development during early pregnancy in rodents and non-human primates. Disruption of VEGF signaling has also been associated with developmental anomalies including poor development of the cranial region, formlins, forebrain, heart, and blood vessels.

Lactation
Risk Summary
There is no information on the presence of ramucirumab in human milk or its effects on the breastfed child or on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential risk for serious adverse reactions in breastfed children from ramucirumab, advise women not to breastfeed during treatment with CYRAMZA and for 2 months after the last dose.

Females and Males of Reproductive Potential
Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to initiating.

Contraception
Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to a pregnant woman.

Females
Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for 3 months after the last dose.

Infertility
Females
Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Pediatric Use
The safety and effectiveness of CYRAMZA in pediatric patients have not been established.

Juvenile Animal Toxicity Data
In animal studies, effects on epiphyseal growth plates were identified. In cynomolgus monkeys, anatomical pathology revealed adverse effects on the epiphyseal growth plate (thickening and osteochondropathy) at all doses tested (5-50 mg/kg). Ramucirumab exposure at the lowest weekly dose tested in the cynomolgus monkey was 0.2 times the exposure in humans at the recommended dose of ramucirumab as a single agent.

Geriatric Use
Of the 563 CYRAMZA-treated patients in REGARD and RAINBOW, 205 (36%) were 65 and over, while 41 (7%) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Of the 221 patients who received CYRAMZA with erlotinib in RELAY, 119 (54%) were 65 and over, while 29 (13%) were 75 and over. Overall, no clinically meaningful differences in effectiveness were observed between these patients and younger patients. Adverse reactions occurring at a 10% or higher incidence in patients receiving CYRAMZA with erlotinib and with a 10% or greater difference between patients aged 65 or older compared to patients aged less than 65 years were: diarrhea (75% versus 65%), hypertension (50% versus 40%), increased ALT (49% versus 35%), increased AST (49% versus 33%), stomatitis (46% versus 36%), decreased appetite (32% versus 19%), dysgeusia (23% versus 12%), and weight loss (19% versus 8%).

Of the 1253 patients in REVEL, 455 (36%) were 65 and over, while 84 (7%) were 75 and over. Of the 627 patients who received CYRAMZA with docetaxel in REVEL, 387 (38%) were 65 and over, while 35 (7%) were 75 and over. In an exploratory subgroup analysis of REVEL, the hazard ratios for overall survival in patients less than 65 years old was 0.74 (95% CI: 0.62, 0.87) and in patients 65 years and over was 1.10 (95% CI: 0.89, 1.36).

Of the 529 patients who received CYRAMZA with FOLFIRI in RAISE, 209 (40%) were 65 and over, while 51 (10%) were 75 and over. Overall, no differences in efficacy were observed between these subjects and younger subjects. Adverse reactions occurring at a 10% or greater difference between patients aged 65 or older compared to patients aged less than 65 years were: diarrhea (75% versus 65%), hypertension (50% versus 40%), increased ALT (49% versus 35%), increased AST (49% versus 33%), stomatitis (46% versus 36%), decreased appetite (32% versus 19%), dysgeusia (23% versus 12%), and weight loss (19% versus 8%).

Additional information can be found at www.cyramza.com

RB-G HCP BS 03JUN2020
Genomic Analyses Enter the Picture in Endometrial Cancers

**APPROACHES TO RISK STRATIFICATION**

in uterine malignancies are evolving, including for endometrial cancers. Genomic markers offer the potential to further identify subsets of patients, according to 2 experts who participated in the OncLive Insights® program “Key Advances in Endometrial Cancer.”

Classic definitions of histology and staging the extent of disease remain important facets of developing a treatment plan, said David M. O’Malley, MD. As a result of the molecular characterization of endometrial cancer, investigators also are looking at categorizing disease by low versus high mutational burden status and genomic aberrations in genes such as TP53 and POLE.

“We’ve learned a tremendous amount in the past 3 to 5 years about the importance of molecular profiling in patients with endometrial cancer, both in early stage and, probably more important, for treatment selection in advanced-stage and recurrent-stage disease,” noted Kathleen Moore, MD. She said all patients with endometrial cancer should have their tumors tested for mismatch repair proteins, with or without microsatellite instability, at the time of diagnosis.

O’Malley is the director of the Division of Gynecologic Oncology at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute in Columbus. Moore is director of the Oklahoma TSET Phase 1 Program at the University of Oklahoma College of Medicine and an associate professor of gynecologic oncology at Stephenson Cancer Center, both in Oklahoma City.

German Specialists Discuss Their Approach to Advanced Melanoma

**PREVIOUSLY, INTERFERON WAS THE standard adjuvant treatment for patients with stage II and III melanoma, but the paradigm in German cancer centers has fully shifted toward combination targeted therapy or immune checkpoint inhibitor monotherapy.**

Dirk Schadendorf, MD, and Axel Hauschild, MD, PhD, made that observation during “Treatment Approaches in Advanced Melanoma,” an OncLive Insights® program.

Schadendorf is the head of dermatology at Essen University Hospital in Essen, and Hauschild leads the dermatology working group at the University Hospital Schleswig-Holstein in Kiel, Germany.

Outcomes data collected over the past 3 to 5 years have established adjuvant therapy with dabrafenib (Tafinlar), a BRAF inhibitor, plus trametinib (Mekinist), a MEK inhibitor, for stage III melanoma with V600E or V600K mutations. Monotherapy with the PD-1 inhibitors pembrolizumab (Keytruda) or nivolumab (Opdivo) are adjuvant therapy options for patients without mutations.

Nevertheless, there are many nuances in treatment recommendations. “I think about aggressiveness and willingness to accept toxicity, and what you want to achieve might be quite different in terms of age as well as comorbidities, preferences, and characteristics the patient might have,” Schadendorf said. Additional tumor characteristics also may help inform decisions that balance the risk of toxicities with the benefits of treatment, he noted.

More extensive molecular analyses may enhance outcomes in the future. “Gene expression profiling of primary tumors could eventually lead to the selection of good and less-good patients [for adjuvant therapy], and there are other markers under discussion, but all of this is experimental at this point,” Hauschild said.
Practices Grapple With an Aging Oncology Workforce

Although the number of oncologists engaged in patient care in the United States has been growing, the cancer community is wrestling with an aging workforce, a lack of racial and ethnic diversity, and a shortage of specialists in rural areas.

Those are among the major trends that emerge from a recent snapshot of the oncology workforce compiled by the American Society of Clinical Oncology (ASCO). The findings come at a time when oncology providers are facing new and continuing pressures related to long hours, staffing issues, and reimbursement—all of which contribute to burnout. At the same time, the coronavirus disease 2019 (COVID-19) pandemic has put tremendous financial and operational strain on oncologists and oncology practices.

In light of these trends, OncologyLive® is undertaking a look at forces shaping the oncology workforce. In this first article, experts discuss the implications of an aging workforce. Future installments will examine diversity issues, physician burnout, and rural oncology care challenges.

by DEBORAH ABRAMS KAPLAN

THE COVID-19 PANDEMIC may have stalled some physician retirements, but some experts are predicting an exodus of oncologists within the next 1 or 2 years. Practice managers are working now to mitigate the impact with both formal and informal initiatives.

Overall, the number of oncologists involved in patient care has gradually grown over the past 10 years, according to a 2020 ASCO report. In 2018, 12,826 physicians were actively practicing as medical oncologists, hematologic oncologists, or hematologists, up from 9765 in 2009. Additionally, 7587 oncology providers identified as gynecologic, pediatric, radiation, or surgical oncology specialists (FIGURE 1).

Concerns about the aging workforce are illustrated by the gap between older versus younger medical oncologists and hematologists. Among these specialists, 19.7% were 64 years or older in 2018 and 12.7% were younger than 40 years, a gap that has widened since 2010 (FIGURE 2).

The prospect of retirements looms over the field, according to Robin T. Zon, MD, a medical oncologist and immediate past-president of Michiana Hematology Oncology (MHO) in Mishawaka, Indiana. She expects migrations to start in late 2021 or in 2022.

“As COVID-19 passes and vaccines become more widespread, there may be a bolus of doctors who retire or transition to new roles over the next 2 years,” Zon said in an interview. “Those who were close to retiring but stayed on to help patients through the crises may be more willing to exit as COVID-19 becomes under control. On the other hand, the lack or severe reduction of preventive services as a result of the pandemic may be enough to sway physicians to stay on, especially if provided time off or staff support incentives. Time will be the judge.”

The impact that retirements may have on oncology care is another question. In 2007, an ASCO report predicted that a shortage of oncologists was likely to develop by 2020 because of a rising demand for cancer services, an aging workforce nearing retirement, and a shrinking pool of new physicians seeking training in internal medicine.

Those concerns were repeated in a 2014 report, which found that the predicted shortage was delayed but still looming. Investigators said demand for services provided by oncologists and radiation
A shortage of oncologists has not materialized so far for several reasons, according to Michael P. Kosty, MD, a hematologist and oncologist who is medical director of Scripps Green Cancer Center in La Jolla, California. Kosty worked with ASCO to develop a system to track workforce information.

"First, the recession of 2007-2008 kept many people in the workforce longer than they had planned," Kosty said in an interview. "For financial or economic reasons, people may not have retired at the time they thought [they would]."

Second, steps to supplement oncology care through increased support for fellowship directors to recruit and train new oncologists and an expanded use of advanced practice providers (APPs) are having a positive impact. Several initiatives to foster interest in the oncology field among medical students have been showing progress.

The proportion of practices employing APPs has grown with at least 5350 and as many as 7000 APPs in oncology positions, according to survey findings reported in 2018.3

"The paradigm that we didn’t foresee in the early 2000s was the employment of advanced practice providers and their integration into cancer care," Kosty said. "Oncology care has evolved from a monolithic single person providing the care to a team-based approach. Nurse practitioners, physician assistants, clinical pharmacists, social workers, etc, have played an increasing important role in patient care."

Although the growth of such professions has eased the burden on the delivery of care, recruiting for oncologists remains challenging. Zon’s practice, like many independent centers, now uses an outside company to help with recruiting.

The pandemic paused or greatly slowed the physician search process, according to
Tom Florence, executive vice president of recruiting for physician search firm Merritt Hawkins, based in Dallas, Texas. Health care systems tried to determine how to address COVID-19 and set up for a large volume of patients. Starting in June 2020, the demand for physician recruitment has increased across medical specialties, he said.

Hematology/oncology is the seventh most requested search field and the first in terms of demand, Florence said. Recruiting takes more time, and practices should start their search earlier than they need to fill a position. “It’s not impossible to recruit somebody; it just can take longer,” Florence said.

RETAINING SPECIALISTS
Although demographic trends for the oncology workforce may not be in their favor, practice managers are looking to other strategies to retain specialists on their staffs.

Oncologists don’t necessarily age out of providing care because of physical limitations, as they might in some surgical specialties, said Debra Patt MD, PhD, MBA, executive vice president of Texas Oncology and a practicing breast cancer specialist in Austin. “I have a lot of partners who are older, or past the average retirement age,” she said in an interview. “It’s a cerebral profession.”

Texas Oncology encourages practices to have programs in place that promote quality in oncology care and track compliance with evidence-based medicine guidelines.

This helps all physicians maintain their knowledge base, but it is especially useful for older oncologists who are not required to sit for board certification maintenance examinations every decade, as are younger colleagues.

The network, which stretches throughout Texas and southeastern Oklahoma, takes a team approach to care that helps lighten the load on oncologists. Texas Oncology has more than 500 oncologists whose work is supplemented with 150 APPs. Patt said that most community practices in the network have a 1:1 ratio of APPs to oncologists. The system has an APP leader and its own executive committee to onboard APPs.

Texas Oncology also sought to be sensitive to staff concerns related to COVID-19. During the early part of the pandemic, the network made a decision to keep older oncologists out of the hospital and allow younger physicians to take their calls. Now, with better screening guidelines and protocols in the hospitals, facilities are safer and there’s less fear among providers about going to work, so physicians are back to their original rounding schedules.

At MHO, several strategies are aimed at attracting new physicians. The practice recently changed its corporate structure to a model where physicians are employees, which helps alleviate the financial risk a doctor faces and allows their focus to be on high-quality, cost-effective care. Although the change was made before the pandemic, the decision was reinforced when some payers delayed reimbursements during the crisis.

“The newer generation wants an employment model,” Zon said. Medical school does not prepare physicians for the financial realities and risks of running an independent practice. Given the costs of oncology treatments, physicians were increasingly uncomfortable being responsible for billing and waiting for reimbursement.

In addition, independent practices are not only competing against academic centers for new physicians but also, potentially, their local hospital. Zon, for example, said a hospital near MHO began hiring its own oncologists. The employment model helps level the playing field for independently owned practices compared with a hospital employment model.

The new approach also allows MHO to hire for part-time work, which may either help retain some oncologists or attract those who don’t want to work full time. It allows physicians who might otherwise retire to mentor younger colleagues and keep their knowledge in the practice.

One development related to the pandemic that might help with oncologist retention is the expansion of telemedicine. If these services continue to be authorized and reimbursed, it could “encourage physicians considering retirement to maintain some involvement in the profession,” Zon said.

Guarding Against Cybersecurity Risks

by LOGAN LUTTON AND TODD SHRYOCK

TECHNOLOGY THAT CONNECTS providers, patients, hospitals, and health systems and allows them to share data is a boon to oncologists managing massive amounts of information. But if hackers get into your system, it can cost you thousands of dollars to repair the damage, pay the HIPAA fines, and rebuild your reputation.

Here are some best practices from the American Medical Association.

1 Protect Your Internet Connection. Install a firewall between your internal network and the Internet. Check with your network professional to make sure everything is turned on and configured properly.

2 Protect Your Wi-Fi Hotspots. The preinstalled password isn’t good enough. If your network has more than 1 component, make sure each has updated software.

3 Protect Windows. If your office computers use Microsoft Windows, they have a software firewall available. Make sure this is enabled.

4 Secure Wi-Fi Access. Mask the identity of the service set identifier (SSID), which is the name of the wireless network, and only provide patients with the Wi-Fi login credentials on request.

5 Limit Wi-Fi Access Times. When setting up the SSID, be sure to encrypt the Wi-Fi networks. This step helps protect office data from electronic eavesdroppers. Consider setting an access schedule for the public Wi-Fi.

6 Use a VPN for Remote Access. Virtual private networks (VPNs) provide the ability to securely connect to your office using a range of devices such as a tablet, PC, or smartphone.

7 Beware of Printers and Copiers. Modern copy machines and printers contain hard drives similar to computers and automatically store a copy of what’s printed or copied. Remove stored data before returning to vendor.

8 Have a Backup. To prepare for the worst, develop and test backup and disaster recovery plans that anticipate how to recover any lost medical and practice records.
Building MOMENTUM for Patients with Myelofibrosis

If you are interested in learning more about the MOMENTUM Clinical Trial for Patients with Myelofibrosis and determining if your patients may be eligible, please contact a MOMENTUM Trial representative by visiting momentumtrial.com/for-physicians
Findings Suggest Cholesterol Plays a Surprising Role in Pancreatic Cancer

by IGOR ASTSATUROV, MD, PhD

ALTHOUGH A MAJORITY OF pancreatic cancer cells are highly dependent on endogenous biosynthesis of cholesterol, new research from investigators at Fox Chase Cancer Center has demonstrated that some more aggressive pancreatic cancers are completely independent of this process.

Disruption of cholesterol biosynthesis by Nsdhl knockout or treatment with statins transforms glandular pancreatic carcinomas in mice to the more aggressive basal subtype via the activation of SREBP1. When SREBP1 is cleaved and goes to the nucleus, this induces Tgfb1 expression, autocrine TGF-β–SMAD2/3 signaling, and epithelial-mesenchymal transition (EMT).

A recent multifaceted investigation by a group of scientists at Fox Chase and collaborators across the United States proved this finding and published the data in "Cholesterol Pathway Inhibition Induces TGF-β Signaling to Promote Basal Differentiation in Pancreatic Cancer," which appeared in the October 2020 issue of the journal Cancer Cell.1

NAVIGATING THE CHOLESTEROL PATHWAY

Pancreatic ductal adenocarcinoma (PDAC) is poised to become the second-leading cause of cancer death in the United States by 2030. The median survival for patients with basal PDAC is much lower than that of the classical subtype (6.3 months vs 10.4 months, respectively), according to data from the COMPASS study (NCT02750657).2

There are 2 major types of pancreatic cancer cells: classic, or glandular, and the more aggressive and treatment-resistant basal. Defined on the basis of transcriptional profiling, classic pancreatic cancer cells tend to grow in clusters and maintain features of epithelial differentiation. The basal variant features cancer cells that look like fibroblasts and are notoriously resistant to chemotherapy, resulting in far shorter life expectancies for patients (FIGURE).

To understand the metabolic dependencies of pancreatic cancer, we initially hypothesized that, by blocking biosynthesis of cholesterol in pancreatic cancer cells, we could suppress tumor development. We took advantage of a genetic mouse model in which we could turn off one of the cholesterol biosynthetic genes, Nsdhl. This protection happened in mice, in which cancer cells retained a single copy of the tumor-suppressor Trp53 gene. However, when the Trp53 gene was completely removed, the protection was lost and, surprisingly, the pancreatic cancer switched from classic to the basal subtype.

To replicate the genetic experiment with a pharmacological cholesterol pathway inhibitor, we next treated mice with a commonly prescribed atorvastatin (Lipitor). In this experiment, we found that tumors pharmacologically deprived of cholesterol exhibit more aggressive, sarcomatoid histology. Analyses by single-cell RNA sequencing were illuminating and allowed us to decipher a potential culprit mechanism that was responsible for the cholesterol pathway-regulated cancer cell differentiation switch.

In Nsdhl-deficient murine pancreatic cancers, we observed remarkable increases in the population of mesenchymal carcinoma cells (we dubbed as EMT cells), which constituted more than 80% of the entire cancer cell population. We noted that in Nsdhl-deficient cancer cells, which maintained epithelial differentiation features, there was a significant increase in the expression of Tgfb1—a growth factor responsible for EMT and a hallmark feature of the EMT subset of pancreatic cancer cells.

Our next task was to explain how the cholesterol pathway blockade could regulate TGF-β signaling. In vitro depletion of cholesterol in cancer cells activated...
Partner Perspectives

a transcriptional factor SREBP1 and unexpectedly induced 
*Tgfβ1* expression. This increased amount of secreted TGFβ1 in the 
culture media triggered the canonical TGF-β signaling cascade in PDAC cells.

We then turned our attention to 55 pancreatic tumor tissue samples of previously 
untreated patients who had undergone surgery for localized pancreatic adenocarcinoma. We compared a sample of patients 
who had not taken statins with 14 patients 
who were routinely taking statins until the 
day of surgery. The abundance of EMT cells and levels of TGF-β signaling in patients 
taking statins was inversely proportionate to 
the level of lipids in the blood.

If patients exhibited high lipids, their 
percentage of EMT cells was low; if their 
cholesterol was low, there was an increase in 
EMT cells. These results suggest that blood 
lipids and blood cholesterol may be involved in 
the regulation of the emergence of more 
aggressive pancreatic cancer cells in tumors.

**CLINICAL IMPLICATIONS**

Because basal tumors are inherently 
treatment-resistant and aggressive, 
identifying this new metabolic regulator that 
can promote the EMT and basal conver-
sion—which is ultimately responsible 
for chemotherapy resistance and meta-
static spread—should help investigators 
overcome a major obstacle for anticancer 
therapy. Based on these data, we also 
obtained a greater appreciation of the intra-
tumoral clonal heterogeneity, in that a given 
human or mouse cancer consists of multiple 
clones of cells. As in mice, human tumors 
contain both mesenchymal (or EMT) and 
epithelial carcinoma cells, as well as some 
subset of cells in between—a whole spect-
trum of clones.

When a tumor is subjected to chemother-
apy and the patient has taken statins, that 
combination may favor the growth of poten-
tially more aggressive cancer cell clones. We 
are just beginning to understand this "clonal 
competition"; the more we supply selective 
pressure to pancreatic cancer cells, the more 
one type of cell predominates. Uncovering 
their respective sensitivities to treatments 
and drugs will deepen our understanding of 
the clonal shifts.

Our results may be relevant for patients 
who should not continue taking statins when 
combating advanced metastatic cancers. In 
fact, I have started critically reviewing 
my patients' medication lists and stop-
ping statins if the potential benefits become 
irrelevant in lieu of their advanced cancer 
diagnosis, especially if their cancer carries 
*Trp53* mutations.

Another unanswered question: Could 
statins act differently in the setting of wild-
type versus mutant *Trp53*? The answer could 
potentially explain why no clear relationship 
has been established between statin use, 
PDAC incidence, and survival. Even more 
speculatively, a precipitous drop in blood 
lipids, which we sometimes observe in cases 
of poor nutrition and cachexia, could contrib-
ute to cancer aggressiveness.

To obtain greater clarity regarding the 
relationship between diet, medication, and 
pancreatic cancer aggressiveness, we are 
beginning to look at a larger collection of 
human samples to determine how blood 
lipids correlate with a patient’s nutrition, 
medicines, and percentage of EMT cells in 
their tumors.

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**Surgical Oncology Is More Than Just Surgery**

**AFTER 15 YEARS AS A SURGEON**, Jeffrey M. Farma, MD, says he’s still learning 
how to treat patients 
with cancer. As fellowship 
director of the Complex 
General Surgical Oncology 
Fellowship at Fox Chase 
Cancer Center, he expects 
his trainees to be prepared to do the same.

“My job is to make my surgical fellows really 
have a full understanding of treating all aspects 
of the patient with cancer,” he said. “That’s my 
ultimate goal.”

A surgical fellowship is different from other 
oncology programs because instead of focusing 
on a single tumor type, the surgeon has to learn 
about all of them. Farma said that an oncological 
surgeon may eventually specialize in a particular 
disease site, but surgeons must come out of 
fellowship with a broad knowledge of many types 
of disease and many areas of the body.

“[Surgical fellows] have to learn when to oper-
ate, but more importantly, when not to operate,” 
said Farma. “That’s a very, very important skill to 
learn. They need to learn how to effectively stage 
and initially evaluate patients for cancer. Then 
after surgery, they have to learn how to follow 
the patients. We generally see all the patients for 
surveillance for years to come.”

Farma expanded to on this to say that fellows 
should have an understanding of the multifaceted 
approach to care. “They need to know how to 
run and manage a clinic and how to run teams— 
leadership, surveillance, and survivorship. They 
also need to know the palliative side of surgical 
oncology, how best to lead and manage difficult 
conversations. These are all aspects that I think 
are really important in the 2-year fellowship. 
“Being a surgeon is a continuum. You don’t just 
finish. I’m still learning and becoming a better 
surgeon every day. But we are, more importantly, 
teaching them how to think about cancer, which 
is the most important thing for me.”

Farma earned his MD at Temple University’s 
Lewis Katz School of Medicine in Philadelphia, 
Pennsylvania, before completing surgical fellow-
ships at the National Cancer Institute in Bethes-
da, Maryland, and Moffitt Cancer Center in Tam-
pa, Florida. He returned to his native Philadelphia 
in 2009 when he joined the Department of 
Surgical Oncology at Fox Chase. He also serves 
as chair of the program directors’ committee for 
the Society of Surgical Oncology.

This article original appeared in *Oncology Fellows*. 
The Many Shades of \textit{KRAS}: Investigators Seek to Exploit Heterogeneity in Mutations

\textit{by Jane De Lartigue, PhD}

\textbf{KRAS HAS TOPPED} the most wanted list of therapeutic targets in oncology for decades, but it has resolutely resisted all efforts, garnering it a reputation as undruggable.\textsuperscript{1} That may change as a historic FDA approval for a first-in-class KRAS G12C inhibitor inches closer. In December 2020, Amgen submitted a new drug application (NDA) to the FDA for sotorasib (AMG 510) for the treatment of patients with \textit{KRAS} G12C-mutated advanced non-small cell lung cancer (NSCLC).\textsuperscript{2}

If approved, sotorasib would represent a significant advance for the approximately 13% of patients with NSCLC whose tumors harbor this specific mutation\textsuperscript{1,5}; with an estimated 228,820 new cases of lung cancer anticipated in the United States in 2020,\textsuperscript{3} nearly 30,000 patients would be eligible for sotorasib therapy.

A second KRAS G12C inhibitor, adagrasib (MRTX849; Mirati Therapeutics, Inc) is hot on sotorasib’s heels, and promising data from the phase 1/2 KRYS TAL-1 trial (NCT03785249), for patients with NSCLC and other cancer types, were recently presented at the 2020 Molecular Targets and Cancer Therapeutics Symposium, hosted by the European Organisation for Research and Treatment of Cancer, National Cancer Institute, and American Association for Cancer Research.\textsuperscript{6,7}

The trade-off with these drugs is that they do not target all \textit{KRAS} mutations, and decades of intensive research have established that \textit{KRAS}-mutant cancers are highly heterogeneous.\textsuperscript{1,8,9}

\textit{KRAS} mutations are common in other cancer types as well as NSCLC, but there is substantial variation in the position and type of mutation (\textbf{FIGURE 1}). In pancreatic ductal adenocarcinoma cases, for example, the vast majority of which harbor \textit{KRAS} mutations, the most common \textit{KRAS} alteration is the G12D substitution.\textsuperscript{8,10}

Investigators are striving to understand the implications of these \textit{KRAS} mutation patterns, with findings from some studies suggesting that they have prognostic implications and may even predict response to therapy. The picture is further complicated by the presence of common co-occurring mutations.\textsuperscript{1,3,11}

The most important question is whether \textit{KRAS} variants other than G12C are amenable to therapeutic targeting, and attention in the field is beginning to move in this direction. Strategies in clinical development include an effort to harness the power of small interfering RNA (siRNA) to inhibit the G12D mutant in pancreatic cancer by encapsulating it in a new drug delivery system, iExosomes.\textsuperscript{12,13} The G12D variant is also the focus of drug discovery efforts by Mirati, which plans to bring its lead compound, MRTX1133, to clinical trials in the next year.\textsuperscript{14}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{kras-mutations.png}
\caption{\textbf{FIGURE.} \textit{KRAS} Variants in Select Tumor Types\textsuperscript{3}}
\end{figure}

\begin{itemize}
\item Clinical investigators are taking a more granular look at \textit{KRAS} mutations, which can vary widely between tumor types. This figure shows the differences in specific \textit{KRAS} alterations in pancreas and lung cancers.
\end{itemize}

\textbf{MUTATION PATTERNS VARY}

\textit{KRAS} proteins are encoded by \textit{RAS} genes, which are among the most common genetic alterations in human cancer. These genes encode 4 highly homologous proteins—\textit{NRAS}, \textit{HRAS}, \textit{KRAS4A}, and \textit{KRAS4B}—which play a vital role in transducing extracellular signals into intracellular ones to elicit cellular responses.\textsuperscript{1}

The \textit{RAS} proteins cycle between an active and inactive state by binding to the small nucleotides guanosine triphosphate (GTP) and guanosine diphosphate (GDP), respectively. Upstream activation of membrane-bound growth factor receptors, such as EGFR, triggers recruitment of a guanine exchange factor to the plasma membrane, which facilitates the exchange of GDP for GTP. GTP-bound \textit{RAS} undergoes a conformational change that allows it to interact with effector proteins in downstream signaling pathways, the best characterized among them being the MAPK pathway, ultimately initiating transcriptional programs in the nucleus that regulate a variety of cellular processes.\textsuperscript{3,15}

\textit{RAS} signaling is terminated by the binding of a GTPase-activating protein that enhances its intrinsic GTPase activity and shifts the balance back to the inactive GDP-bound state. Oncogenic mutations in the \textit{RAS} genes lock the protein in the GTP-bound form, allowing the cancer cell to exploit the downstream overactivation of growth signaling pathways.\textsuperscript{3,15}

Despite the similarity in the sequence and function of \textit{RAS} genes, there is considerable...
variation in the frequency and distribution of RAS mutations across cancer types. KRAS is by far the most commonly mutated of the 3 genes (~85% of cancer cases), but NRAS mutations (~11% overall) are enriched in melanoma. HRAS mutations, despite having the lowest prevalence overall (~7%), are most common in cancers of the bladder, thyroid, prostate, and head and neck.16,17

KRAS is most highly mutated in pancreatic cancer (>90% of cases), colorectal cancer (CRC; 30%-40% of cases), and NSCLC (15%-20% of cases), but other common cancer types include ovarian and endometrial cancer. KRAS mutations can be found less frequently in a variety of other cancers.8

There are several hotspots within the RAS genes at which oncogenic mutations frequently occur, most commonly in codons 12, 13, 61, 117, and 146. However, the relative frequency also varies between the 3 isoforms,1,7 with codon 12 mutations the dominant form for KRAS and codon 61 for NRAS.8

The specific substitutions observed at each codon even vary across different cancer types. In NSCLC, KRAS G12C mutations (with a glycine-to-cysteine substitution) are the most common, whereas in pancreatic cancer and CRC, the G12D (glycine to aspartate) substitution is more prevalent. CRC is notable for the diversity of KRAS mutations associated with it; mutations at K117 and A146, for example, are rare overall but are found with a significant frequency in CRC.18

HOW, WHY, AND WHAT IT MEANS
Growing appreciation of the complexity of KRAS-mutant cancers leads to the inevitable questions of why such variability in mutated alleles exists, what drives it, and, above all, what the potential implications are.

At the molecular level, RAS-mutation hotspots are found around the nucleotide-binding pocket and result in enhanced GTP binding and accumulation of activated RAS. But evidence suggests that the precise mechanisms through which this occurs differ somewhat depending on the type of mutation.2,18

Codon 12 and 61 mutations affect hydrolysis, but not the rate of nucleotide exchange, whereas mutations in codons 13 and 117 affect both. Conversely, rarer codon 146 mutations affect nucleotide exchange, but not hydrolysis. Different KRAS mutants have also been shown to differentially alter the affinity of the mutant protein for downstream effectors.18 As a result, although all KRAS mutations are activating, their oncogenic potential varies, and this may impact patient prognosis and therapeutic outcomes.

The presence of KRAS mutations has generally been shown to be associated with poorer patient prognosis in NSCLC, CRC, and pancreatic cancer, but there have been conflicting reports. More recently, efforts have focused on unraveling the potential influence of individual KRAS mutation subtypes, and the results suggest that the prognostic value of a KRAS alteration may depend on which specific mutant is present and the type of cancer. For example, although codon 12 mutations are associated with decreased survival in CRC, results of some studies have shown similar outcomes for patients with codon 13 mutations and those with wild-type KRAS.3,18

The predictive value of KRAS mutations has been examined in a number of studies. Some findings indicate a negative association in specific cancer types between certain KRAS mutations and response to chemotherapy, various types of targeted therapy, and immunotherapy, but there is currently little consensus on this.3,18

### TABLE. Clinical Development of KRAS Mutant–Specific Inhibitors

<table>
<thead>
<tr>
<th>Drug (sponsor/collaborator)</th>
<th>Description</th>
<th>Phase Clinical trial name/Clinicaltrials.gov identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS G12C inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotorasib (AMG 510) (Amgen)</td>
<td>Vs docetaxel in previously treated locally advanced and unresectable or metastatic KRAS G12C–mutant NSCLC</td>
<td>Phase 3 CodeBreak 200/NCT04303780</td>
</tr>
<tr>
<td></td>
<td>In KRAS G12C–mutant advanced nonsquamous NSCLC</td>
<td>Phase 2 Lung-MAP cohort/NCT04625647*</td>
</tr>
<tr>
<td></td>
<td>+/- a PD-1/PD-L1 inhibitor in KRAS G12C–mutant advanced solid tumors</td>
<td>Phase 1/2 CodeBreak 100/NCT03600883</td>
</tr>
<tr>
<td></td>
<td>+/- various different drugs in KRAS G12C–mutant advanced solid tumors</td>
<td>Phase 1 CodeBreak 101/NCT04185883</td>
</tr>
<tr>
<td>Adagrasib (MRTX849) (Mirati Therapeutics, Inc)</td>
<td>+ pembrolizumab in KRAS G12C–mutant advanced NSCLC</td>
<td>Phase 2 KRYSTAL-7/NCT04613596</td>
</tr>
<tr>
<td></td>
<td>+/- cetuximab, afatinib, or pembrolizumab in KRAS G12C–mutant advanced solid tumors</td>
<td>Phase 1/2 KRYSTAL-1/NCT03785249</td>
</tr>
<tr>
<td>GDC-6036 (Genentech, Inc)</td>
<td>+ TNO155 (SHP2 inhibitor) in KRAS G12C–mutant advanced solid tumors</td>
<td>Phase 1/2 KRYSTAL-2/NCT04330664</td>
</tr>
<tr>
<td>Exosomes engineered to deliver siRNA targeting KRAS G12D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>iExosomes (The University of Texas MD Anderson Cancer Center)</td>
<td>In KRAS G12D–mutant metastatic pancreatic cancer</td>
<td>Phase 1 2018-0126/NCT03608631*</td>
</tr>
<tr>
<td>mRNA vaccine targeting KRAS G12C, G12D, G12V, and G13D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRNA-5671 (Moderna Therapeutics/Merck)</td>
<td>+/- pembrolizumab in KRAS G12C–, G12D–, G12V–, or G13D–mutant advanced metastatic NSCLC, CRC, or pancreatic adenocarcinoma with specific HLA subtypes</td>
<td>Phase 1 V941-001/NCT03948763</td>
</tr>
<tr>
<td>T cells transduced with KRAS G12V–specific TCRs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS TILs (Changhi Hospital/Providence Cancer Center, Earle A. Chiles Research Institute)</td>
<td>In KRAS G12V–mutant advanced pancreatic cancer with a specific HLA subtype</td>
<td>Phase 1/2 Changhai-H-PP06/NCT04146298</td>
</tr>
</tbody>
</table>

CRC, colorectal cancer; HLA, human leukocyte antigen; NSCLC, non–small cell lung cancer; siRNA, small interfering RNA; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte.

*Trial is not yet recruiting participants.
The clearest role for KRAS as a predictive biomarker is in identifying patients with CRC who will not respond to EGFR-targeted therapy, but even this may be affected by the specific mutant allele. According to findings from some studies, although patients with CRC harboring most KRAS mutations are insensitive to EGFR inhibitors, KRAS G13D-mutant tumors may actually respond to these agents. This may be partly explained by the observation that the G13D mutation induces EGFR expression.18,39

The picture is further complicated by the common co-occurrence of other mutations along with KRAS, including those in STK11, KEAP1, CDKN2A/B, and TP53, which may themselves affect prognosis and response to therapy.9,20

**MUTANT-SPECIFIC INHIBITORS**

After decades of failed attempts to target the RAS pathway, which came to be thought of as undruggable, greater insight into KRAS biology has led to the discovery of potentially targetable pockets on the mutant protein.1,3,21 Signals of efficacy in several novel agents have spurred fresh industry research into KRAS-specific targets (TABLE).

Several small-molecule inhibitors of the KRAS G12C-mutant protein have been developed and represent a promising advance in the treatment of KRAS-mutant cancers. These drugs bind to a small pocket underneath the effector binding region that is only revealed in the GDP-bound form, locking the mutant protein in this inactive state.1,3

Leading the pack is sotorasib, which investigators are evaluating in clinical trials in various KRAS-mutant cancers and which has advanced the furthest in NSCLC. Amgen submitted an NDA for sotorasib for the treatment of patients with KRAS G12C-mutant advanced NSCLC, according to a company announcement in December 2020.2

The submission is supported by phase 2 results from the ongoing CodeBreak 100 study (NCT03600883) in patients with disease progression after up to 3 prior lines of therapy. Orally administered sotorasib resulted in median progression-free survival of 6.8 months (95% CI, 5.1-8.2) with a confirmed objective response rate (ORR) of 37.1% among 124 patients. The findings were presented during the International Association for the Study of Lung Cancer World Conference on Lung Cancer in January 2021. The phase 3 confirmatory CodeBreak 200 trial in NSCLC recently began enrolling patients (NCT04303780).3,23

Mirati Therapeutics has also advanced its KRAS G12C inhibitor into clinical trials. As of August 30, 2020, 108 patients with previously treated advanced solid tumors (79 NSCLC, 22 CRC, and 7 other) had been treated with adagrasib 600 mg twice daily.6,7

The ORR in patients with NSCLC was 45%, including 5 unconfirmed partial responses (PRs), and in patients with CRC it was 17%. Confirmed PRs also were observed in 1 patient with endometrial cancer and in another with pancreatic cancer. Treatment-related adverse events included nausea, diarrhea, vomiting, fatigue, and increased alanine aminotransferase levels.6,7

**BEYOND G12C**

Although they undoubtedly represent a big leap forward for RAS-mutant cancers, KRAS G12C inhibitors have several key limitations that are spurring ongoing drug development efforts.

Investigators have already identified several mechanisms of resistance to KRAS G12C inhibitors. These include drug-induced selection for cells with upstream upregulation of EGFR, which maintains KRAS in the inhibitor-insensitive GTP-bound state.24 Inhibitors of the GTP-bound form are highly sought after, but their development is challenging due to the lack of potential drug binding sites.

Revolution Medicines developed its novel technology to meet this challenge. The company’s small-molecule inhibitors drive formation of a 3-protein “tri-complex” with KRAS G12C and a chaperone protein, which creates a novel binding pocket for the drug. This process also indirectly inhibits oncogenic KRAS signaling because the chaperone protein blocks KRAS G12C from interacting with downstream effectors.25

In a presentation at the RAS Targeted Drug Development Summit in September 2020, Steve Kelsey, president of research and development at Revolution Medicines, reported promising preclinical data for the company’s KRAS G12C(ON) and KRAS G12D(ON) inhibitors.26

Another limitation of KRAS G12C inhibitors is that they only target the G12C mutation; they don’t target other substitutions that are more common in other types of cancer, such as G12D, which would be a prime target for pancreatic cancer therapy.28

Mirati is developing a KRAS G12D inhibitor, MRTX1133, which has demonstrated significant tumor regression in preclinical models. The company reportedly plans to file an investigational NDA with the FDA in the first half of 2021.14

RNA interference (RNAi) also is a promising method for regulating the expression of target genes, particularly those that are not amenable to targeting by conventional drugs, such as KRAS. However, effective delivery of siRNA (a type of RNAi molecule) to the cancer site is challenging.27

Investigators are exploring the use of exosomes—small, fluid-filled, membrane-bound sacs that bud off from the cell surface and play a physiological role in transporting waste or cellular cargo—as a novel drug delivery system. iExosomes are exosomes that have been engineered to act as vehicles for siRNA targeting a gene of interest.

They are similar to liposomes and other nanoparticle drug delivery systems in development, but they express the cell-surface protein CD47, which generates the so-called “don’t eat me” signal upon receptor binding. This allows them to avoid phagocytosis by immune cells, which should extend their half-life in the circulation. Preclinical development of iExosomes targeted KRAS G12D-mutant pancreatic cancer, and a phase 1 trial (NCT03608631) is underway.12,33

Also in clinical trials are several agents based on immunotherapeutic strategies targeting mutant KRAS proteins. Merck and Moderna are developing mRNA-5671, a cancer vaccine designed to target the *KRAS* G12C, G12D, G12V, and G13D mutants. Meanwhile, the use of adoptive cell therapy is also being explored, with genetically engineered T-cell receptors that recognize the G12V and G12D mutants transduced into tumor-infiltrating lymphocytes and peripheral blood lymphocytes, respectively.26

For a full list of references, see the article at OncLive.com.
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At Cedars-Sinai, the dedication of our doctors and staff has made us one of the most recognized hospitals in the nation. We’re proud to have earned a place on U.S. News & World Report’s Best Hospitals Honor Roll. This recognition belongs to our entire team who shows up day after day, night after night, to care for patients from around the world.

Learn more about our cancer care: cedars-sinai.org/cancer
Frontline ICI Therapy Gains Traction Across NSCLC Settings

by CHRISTINA T. LOGUIDICE

**TREATMENT STRATEGIES FOR PATIENTS** with advanced-stage non–small cell lung cancer (NSCLC) have shifted away from platinum-based doublet chemotherapy and toward combination strategies that include immune checkpoint inhibitors (ICIs). Data from the KEYNOTE-024 trial (NCT02142738) showed an overall survival (OS) benefit with pembrolizumab (Keytruda) in patients with advanced-stage NSCLC and PD-L1 expression on at least 50% of tumor cells.1 The data led to the first approval of an ICI for patients with PD-L1–positive advanced NSCLC, and since then a variety of ICIs have been showing increasing benefit across larger subsets of patients in the first-line setting, including those without PD-L1 expression, especially when used as part of a combination regimen.

During a recent OncLive Peer Exchange®, a panel of thoracic cancer experts convened to discuss several important immune-oncology (I/O) studies presented during key meetings in 2020, including the European Society for Medical Oncology (ESMO) Virtual Congress 2020 and the 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Program. The panelists reviewed the data, their key takeaways from the regimens assessed, and how these regimens may impact clinical practice in the future.

**ONO-4538-52: NIVOLUMAB/CARBOPLATIN/PACLITAXEL/BEVACIZUMAB**

ONO-4538-52 (NCT03117049) is a randomized phase 3 trial assessing nivolumab (Opdivo) in combination with carboplatin, paclitaxel, and bevacizumab (Avastin) as a first-line treatment for patients with advanced or recurrent NSCLC who do not have EGFR or ALK alterations and could have any level of PD-L1 expression.2 “There are a lot of parallels between the regimen used here and the approved IMpower150 (NCT02366143) regimen, which builds on the backbone of carboplatin/paclitaxel/bevacizumab, showing that when you add atezolizumab [Tecentriq], outcomes were improved,” Stephen V. Liu, MD, said.

“[Investigators of ONO-4538-52 used] a similar approach, except instead of the PD-L1 antibody atezolizumab, [they] used the PD-1 inhibitor nivolumab,” he explained.

All patients in the study received carboplatin/paclitaxel/bevacizumab and were then randomized 1:1 to receive concurrent nivolumab (n = 275) or placebo (n = 275). Following induction therapy, all patients received maintenance bevacizumab and continued either nivolumab or placebo.

At the interim analysis, which occurred after a median follow-up of 13.7 months, progression-free survival (PFS) was significantly improved in the nivolumab arm versus the placebo arm, with a PFS of 12.1 months versus 8.1 months, respectively (HR, 0.56; 95% CI, 0.43-0.71; P < .0001). The objective response rates (ORRs) were 61.5% and 50.5% in these treatment arms, respectively. The OS data were not mature but trended toward benefit with nivolumab (25.4 vs 24.7 months; HR, 0.85; 95% CI, 0.63-1.14). Despite the unclear survival benefit, Liu said the preliminary data suggest there is “some signal” that when you add nivolumab to the carboplatin/paclitaxel/bevacizumab backbone, you can improve outcomes.
**WJOG @BE STUDY: ATEZOLIZUMAB/BEVACIZUMAB**

WJOG @Be Study is a phase 2 Japanese study evaluating the doublet of atezolizumab plus bevacizumab in 40 patients with NSCLC and high PD-L1 expression (≥ 50%). The study’s primary end point was ORR and secondary end points included PFS, duration of response (DOR), OS, and safety. “This trial fell under the radar,” Liu said, but he noted it had impressive end point data with an ORR of 64%. However, all responses were partial responses, with 28% of patients having stable disease and just under 8% having progressive disease. Patients had a median PFS of 15.9 months (95% CI, 5.65-15.93), with a median duration of response of 10.4 months (95% CI, 4.63-NR). “We have a 1-year PFS rate of 55%, which is quite impressive,” Liu said. The 1-year OS rate was 70.6% (95% CI, 50.5%-83.4%).

“I would have loved to have seen a second arm with atezolizumab monotherapy to really see how this stands up. But those high response rates suggest that there may be synergy between these 2 pathways,” Liu said.

**ANTIANGIOGENIC/ANTI-VEGF/ICI COMBINATIONS: POISED TO CHANGE CLINICAL PRACTICE?**

“The whole concept of combining antiangiogenic or anti-VEGF targeted therapies with immune checkpoint inhibition is something that’s widely pursued not just in lung cancer, but many other cancers,” Suresh Ramalingam, MD, said.

“I still have difficulties finding the role for bevacizumab in the first-line setting, and I personally haven’t used it much,” Martin F. Dietrich, MD, PhD, said, noting concerns over the cumulative toxicity, especially when used as part of a quadruplet therapy. In the ONO-4538-52 study (NCT03117049), serious treatment-related adverse effects (AEs) were significantly more common in the nivolumab arm than in the placebo arm, occurring in 41.8% of patients and 26.9% of patients, respectively. “I would like to understand in the first-line setting what’s the contribution to efficacy,” Dietrich said.

The participants agreed that although the WJOG @Be study data are promising, they require verification in larger studies.

**TABLE. ORR by PD-L1 Expression Level in the EMPOWER-Lung 1 Study**

<table>
<thead>
<tr>
<th>PD-L1 expression</th>
<th>Cemiplimab (n = 283)</th>
<th>Chemotherapy (n = 280)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 90%</td>
<td>45.9% (35.8-56.3%)</td>
<td>18.1% (10.9%-27.4%)</td>
</tr>
<tr>
<td>&gt; 60% to &lt; 90%</td>
<td>39.3% (29.1-50.3%)</td>
<td>20.0% (12.3%-29.8%)</td>
</tr>
<tr>
<td>≥ 50% to 60%</td>
<td>32.3% (23.1-42.6%)</td>
<td>22.9% (15.0%-32.6%)</td>
</tr>
<tr>
<td>50% or unknown</td>
<td>26.0% (16.5%-37.6%)</td>
<td>21.6% (12.9%-32.7%)</td>
</tr>
</tbody>
</table>

ORR, objective response rate.

“I would like to see that confirmed with randomization against atezolizumab, which the [study investigators] pointed out, is something that’s planned,” Christine Bestvina, MD, said. “When we talk about triplet therapy, chemotherapy plus immunotherapy in the patients with high PD-L1 expression, one of the arguments that providers will make for using the triplet over monotherapy is if a high response rate is needed, you may choose the triplet. But with seeing this high response rate with the addition of bevacizumab to atezolizumab, I wonder if we’ll be able to use angiogenesis inhibitors in a similar fashion, while still sparing more traditional chemotherapy agents,” she said.

**EMPOWER-LUNG 1 STUDY: CEMIPLIMAB**

EMPOWER-Lung 1 (NCT03088540) is a phase 3 trial comparing the newer PD-1 inhibitor cemiplimab-rwlc (Libtayo) with investigator’s choice of platinum-doublet chemotherapy in 710 treatment-naïve patients with advanced NSCLC who have high PD-L1 expression (≥ 50%) and no EGFR, ALK, or RAS mutations.1 The primary end points were OS and PFS and the secondary endpoints included ORR, DOR, health-related quality of life, and safety. “Randomization to a PD-1 inhibitor versus chemotherapy may sound familiar,” Liu said, adding that this is a similar design to the KEYNOTE studies, including the landmark KEYNOTE-024 trial.

EMPOWER-Lung 1 met its primary and secondary end points. In the intention-to-treat population with PD-L1 of at least 50%, the median OS was not reached in the cemiplimab arm (n = 283) and was 14.2 months in the chemotherapy arm (n = 280; HR, 0.57; 95% CI, 0.42-0.77; P = .0002). The median PFS was 8.2 months versus 5.7 months in these arms, respectively (HR, 0.54; 95% CI, 0.43-0.68; P < .0001). The ORR corresponded with patients’ PD-L1 expression levels in the cemiplimab arm (TABLE).

“Cemiplimab had a better response rate, a better PFS, better overall survival, and a better toxicity profile—a winner across the board. This was despite having a high crossover rate, in fact, higher than what we saw in KEYNOTE-024. The crossover rate in this study was 74%,” Liu said. Patients in the cemiplimab arm had significantly fewer treatment-related AEs, including grade 3 to 5 AEs (37.2% vs 48.5%). The panelists noted that an interesting feature of EMPOWER-Lung 1 was that 45% of patients had squamous cell carcinomas. When examining OS events in these patients compared with those who had nonsquamous tumors, the panelists were not surprised to see that those with squamous histology showed greater benefit.

“Squamous cell carcinoma is a more immunotherapy-sensitive disease. The correlation with smoking, higher tumor mutational burden, and inflammatory markers is probably more stringent than for adenocarcinomas,” Dietrich said. There was some question whether all checkpoint inhibitors would demonstrate similar outcomes, but the panelists agreed that the overall medical literature indicates that squamous cell carcinomas tend to respond better to these agents regardless of which one is being used, and

**Emotionally and physically draining**

The real costs, in terms of emotional and physical drain, can’t be overstated, said Dietrich. Patients may develop resistance to chemotherapy as they treat disease and it’s necessary to change treatment methods. "We need to change our paradigm of how we treat lung cancer," he said.}

**The panelists agreed that the overall medical literature indicates that squamous cell carcinomas tend to respond better to these agents regardless of which one is being used, and**
that PD-1 or PD-L1 expression status and histology play a lesser role in the setting of combination regimens.

“The crossover rate was high, and despite that, the survival advantage was still seen. One might argue that if you delayed initiation of immunotherapy, then patients may not do as well. You can add a checkpoint inhibitor down the road after they’re done with chemotherapy, but we’re seeing more evidence that the earlier you adopt immunotherapy, the better the outcomes are,” Firas B. Badin, MD, said.

Liu agreed and added that while he is in favor of an approval, he is unsure of how or if he would use the agent for patients in his practice. “I don’t know if I see data that are compelling enough to make me change my practice, but I’d absolutely support combinations building on this or using this as a control in a randomized trial,” he said.

**CHECKMATE 227: NIVOLUMAB/IPILIMUMAB**

Ramalingam presented the updated 3-year efficacy and safety data from the CheckMate 227 trial (NCT02477826), in which patients with PD-L1 expression of at least 1% (part 1a) were randomized 1:1:1 to nivolumab/ipilimumab (Yervoy), chemotherapy, or nivolumab monotherapy, and those with PD-L1 expression less than 1% (part 1b) were randomized 1:1:1 to nivolumab/ipilimumab, chemotherapy, or nivolumab/chemotherapy.³ None of the study participants had sensitizing EGFR mutations or known ALK alterations. The primary end points were PFS in patients with high tumor mutational burden (≥10 mut/Mb) and OS in patients with PD-L1 of at least 1%.

“The number that comes to my mind is the 3-year survival rate for patients treated with ipilimumab and nivolumab, which was 33%, both in the PD-L1 high and low group. This is remarkable considering that not too long ago, we were not talking about 3-year survival rates for patients with lung cancer,” Ramalingam said. He noted that the durability of response was also 3- to 4-fold higher compared with chemotherapy. “If patients had a response with chemotherapy, the duration of response was 6.5 months. With ipilimumab and nivolumab, the response duration was almost 23 months. This suggests that patients who derive response with this combined immunotherapy approach can maintain that benefit for a lot longer,” he said.

Based on the CheckMate 227 data, nivolumab/ipilimumab was approved by the FDA in May 2020 as a first-line treatment for patients with metastatic NSCLC whose tumors express PD-L1 (≥1%), as determined by an FDA-approved test, and who have no EGFR or ALK genomic tumor aberrations.⁴ Ramalingam said the National Comprehensive Cancer Network guidelines also recommend nivolumab/ipilimumab for patients with PD-L1-negative tumors.⁵

**CHECKMATE 9LA: NIVOLUMAB/IPILIMUMAB/CHEMOTHERAPY**

CheckMate 9LA (NCT03215706) is a phase 3 randomized, open-label study comparing nivolumab/ipilimumab plus 2 cycles of chemotherapy (n = 361) with 4 cycles of chemotherapy (n = 358) in the first-line setting for patients with advanced NSCLC.⁴ “This is a novel approach,” Badin said. “We’ve never done just 2 rounds of chemotherapy. We tend to do 4 to 6 cycles. That’s the standard in our clinic. But it’s a novel approach with only 2 doses of chemotherapy, trying to get some of the synergy from chemotherapy, plus nivolumab and ipilimumab, and then patients will go into nivolumab/ipilimumab maintenance.”

CheckMate 9LA met its primary end point at the preplanned interim analysis (minimum follow-up, 8.1 months), with a median OS of 14.1 months for nivolumab/ipilimumab/chemotherapy versus 10.7 months with chemotherapy (HR, 0.69; 96.7% CI, 0.55-0.87; P = .0006). When the follow-up interval was extended to a minimum follow-up of 12.7 months, the median OS was 15.6 months with nivolumab/ipilimumab/chemotherapy versus 10.9 months with chemotherapy (HR, 0.66; 95% CI, 0.55-0.80). The magnitude of benefit with the nivolumab combination was consistent across tumor histology and PD-L1 expression levels.

Dietrich said this trial was originally criticized for being too complex but added that it provided some valuable lessons. “Ipilimumab/nivolumab can be competitive in the PD-L1 positive space as a combination, and it can be competitive against chemioimmunotherapy in the PD-L1-negative space. This is going to be hard to argue that this wouldn’t be a strong consideration for every patient in the PD-L1 continuum,” he said.

**I/O-I/O IN THE FRONT LINE: WHERE DOES IT FIT IN?**

Liu said an I/O-I/O approach is an appealing one, especially for patients who are interested in chemotherapy-free regimens. However, he said he is quick to explain to patients that these regimens are not free of AEs and that the grade 3 event rate is comparable to that of chemotherapy. “You won’t necessarily see the myelosuppression, the alopecia, the nausea that we may see with cytotoxic chemotherapy, but there are still a lot of other toxicities we need to be aware of. I need to find the right patients to use that [approach],” he said.

Nevertheless, he said there are several reasons he would opt to use a dual checkpoint blockade regimen up front. “The hazard ratio in the PD-L1 negative space is compelling,” he said. He also noted that it gives him an additional treatment line. “If all things are equal and you start with dual checkpoint blockade, and if it doesn’t work, if you’re not in that group where you get that long-term survival, now my second-line option is platinum doublet chemotherapy, which I would consider an upgrade over standard second-line docetaxel-based therapies,” he said.

Bestvina agreed with this assessment. “I’ve seen the benefit [in patients] with a 0% expression of PD-L1, seeing the benefit that they can obtain with this dual checkpoint blockade is quite impressive...[and] you get to save an amazing second-line option of carboplatin/pemetrexed, which has been the backbone of management for these patients for the prior 10 to 20 years,” she said.

Badin reminded the panel that the CheckMate 9LA regimen can strike a balance and be a good option for some patients as well. “If you don’t want to miss the opportunity of using chemotherapy in the first-line setting, but at the same time you don’t want to give the full force of 4 to 6 cycles, then here is another option for our patients,” he said.
JOSEPH V. SIMONE, MD, a pioneering clinical investigator and institutional leader in pediatric oncology, died January 21, 2021, in Sandy Springs, Georgia. He was remembered as a talented and caring Renaissance man whose work had a broad impact on cancer care, his community, and his colleagues. A 2017 Giants of Cancer Care® award winner, Dr Simone was 85 years old.

During a career that spanned more than 60 years, Dr Simone was best known for his role in the research efforts that resulted in the first curative combination therapy for children with acute lymphoblastic leukemia. As an administrator, he helped craft policies and protocols that enhanced care throughout the oncology field. He developed the initial concept for the Quality Oncology Practice Initiative for the American Society of Clinical Oncology (ASCO).

A native of Chicago, Illinois, Dr Simone began his career in internal medicine before developing an interest in hematologic diseases. In 1967, he took a job at the recently opened St Jude Children’s Research Hospital in Memphis, Tennessee, where he was associate director for clinical research before serving as director and CEO from 1983 to 1992. In 1983, under Dr Simone’s leadership, the hospital was designated as the first National Cancer Institute cancer center dedicated entirely to children.

Dr Simone helped shape the groundbreaking Total V combination chemotherapy and radiation therapy regimen, which raised survival rates for pediatric acute lymphoblastic leukemia from 4% to 50%. James R. Downing, MD, president and CEO of St Jude, credited Dr Simone with establishing the hospital’s HIV/AIDS clinical program and praised him as an extraordinary leader who elevated the center’s basic science programs “to unprecedented heights.”

In another project, Dr Simone worked with colleagues to improve access to care for children through a clinic that also provided nutritional supplements. This led to the formation of the US Department of Agriculture’s Special Supplemental Nutrition Program for Women, Infants and Children. “Our hospital—in truth, the world—owes a great debt of gratitude to Dr Simone for his many accomplishments,” Downing said in a statement. “Dr Simone was a visionary and a world-class clinician and, most importantly, a man of principle. We extend our deepest sympathies to his family, friends, and colleagues.”

Dr Simone’s success in building St Jude as a cancer center had institutions knocking at his door. He served as physician in chief of Memorial Sloan Kettering Cancer Center in New York, New York, from 1992 to 1996. From there, his career path took him to the Huntsman Cancer Institute at the University of Utah in Salt Lake City, where he was the first senior clinical director.

In addition to his leadership roles at cancer centers, Dr Simone served as medical director and chair of the National Comprehensive Cancer Network. “Dr Simone, throughout his remarkable career and in a variety of leadership roles, modeled integrity, empathy, and caring,” Clifford A. Hudis, MD, FACP, FASCO, CEO of ASCO, said in an article posted on the organization’s website. “Among many other contributions, he envisioned and laid the foundation for ASCO’s portfolio of quality programs that improve care for patients everywhere.”

“The health care and oncology communities truly lost a remarkable person,” said Mike Hennessy Jr, president and CEO of MJH Life Sciences®, which sponsors the Giants of Cancer Care® awards program. “It takes a special person to be a pediatric oncologist and he certainly was one.”

One of the biggest challenges for a pediatric oncologist, Dr Simone said in a 2017 interview, is working with patients and their families to understand illness and outcomes. Communicating with children is particularly challenging, he noted. “We use words and concepts that the kids will understand,” Dr Simone said. “It’s tricky, though, because you can scare them: the parents are scared—and sometimes I am scared.”

Despite the difficulties of treating children with cancer, Dr Simone said he never regretted his decision to specialize in the field. “There is no question in my mind that my biggest impact in my career was developing treatments for childhood leukemia. Everything is dwarfed against that,” Dr Simone said. “I think that having become a pediatric oncologist was a godsend for me.”

Among his colleagues, Dr Simone was known as a mentor and adviser who was generous with his time and who recruited many talented physicians. In his obituary, his family shared poignant memories of his dynamic personality: “Joe loved crossword puzzles, the Cubs, old war movies, hardware stores with wooden floors, classical music, homegrown tomatoes, the long hikes and runs of his younger years, the dignity and nobility of a job well done, short homilies, and a good cup of coffee. A self-described curmudgeon, he did not like long plane rides, lingering after a meal, kerfuffles of any variety, late-night dance parties, scorched coffee, or kale.”

He is survived by his wife of 60 years, Patricia Simone; 3 daughters, Pattie Simone (Rob Schreiner), Julie Simone (Stephen Carr), and Margaret Simone (Jeff Maynard); 5 grandchildren; and extended family members.
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