NEW ROLES FOR LEADERS. In a joint interview, Tennessee Oncology's Natalie Dickson, MD, and Stephen Schleicher, MD, MBA, discuss their new titles of chief strategy officer and chief medical officer, respectively. Dickson remains president at Tennessee Oncology, SP72.

PREVENTING COVID-19. Revised guidelines from the National Comprehensive Cancer Network (NCCN) for prevention of COVID-19 among patients being treated for cancer include specifics for those who are considering treatment with chimeric antigen receptor T-cell therapy, SP63.

ZANUBRUTINIB PREFERRED. Changes to the NCCN guidelines in chronic lymphocytic leukemia and small lymphocytic leukemia give preference to the Bruton tyrosine kinase inhibitor zanubrutinib for several groups of patients, including some receiving first-line therapy, SP67.

FOUR-DRUG REGIMENS. Ray Bailey, BPharm, RPh, of Florida Cancer Specialists Pharmacy Services, describes how to evaluate which patients should receive quad therapy in multiple myeloma, SP64.

EMERGENCE OF CDK4/6 INHIBITORS. UCLA Health's Nicholas McAndrew, MD, MSCE, explains how these therapies have changed the treatment landscape in HR+/HER-negative breast cancer, SP66.

STRONGER STANDS. An expert offers reasons why biosimilar developers need to take stronger stands with FDA on efficacy testing, which delays bringing products to market, SP75.

PAYMENT MODELS
Alternative Payment Models Can Stabilize and Improve Practice Radiation Reimbursement

HOW VALUE-BASED CARE IS CHANGING RADIATION ONCOLOGY FOR THE BETTER
Courtney Dean, MBA

TODAY'S EVOLVING HEALTH CARE landscape has created a challenging environment for radiation oncologists—one that makes revenue streams unpredictable and increases the administrative hassle associated with the delivery of quality care. Medicare radiation reimbursement rates declined 24% from 2008 to 2017, with an initial 7% to 8% additional payment cut projected for 2022 based on an American Society for Radiation Oncology (ASTRO) analysis of the 2022 Medicare Physician Fee Schedule,1 which was subsequently mitigated by The Protecting Medicare & American Farmers from Sequester Cuts Act signed in December 2021.2 Cuts to radiation therapy reimbursement are recommended yearly by CMS.

CONTINUED ON SP80 »

PRACTICE TRANSFORMATION
Telehealth at Minnesota Oncology: Tackling COVID-19, Educating Patients, and Overcoming the Weather
Mary Caffrey

THE RISE OF TELEHEALTH during the COVID-19 pandemic has been an important topic at oncology conferences, with surveys showing various levels of satisfaction on the part of providers and patients, as well as concerns about disparities in the level of access to technology.3,4

Reimbursement barriers to telehealth adoption came down during COVID-19, allowing oncology practices to see for the first time where its use made sense and where it did not. The American Society of Clinical Oncology (ASCO) responded with guidelines for telehealth use, suggesting that the technology likely will be part of the treatment landscape for good.5

A consensus is emerging. When it comes to diagnosing cancer, tele-health can never replace the in-person visit. But during a pandemic, it is highly useful—and perhaps better—for some elements of cancer care, because it can increase the number of touch points in areas such as survivorship care and nutrition, which would otherwise require a separate visit to the office.

For some practices, however, telehealth could prove a game changer when dealing with a problem that no quality measure or technology upgrade can fix: the weather.

CONTINUED ON SP84 »

IMMUNO-ONCOLOGY
With Approval for Axi-cel in Second-line on the Horizon, CAR T-Cell Therapy Poised to Enter New Phase
Mary Caffrey

WHEN THE FDA APPROVED the first 2 chimeric antigen receptor (CAR) T-cell therapies in late 2017, the scientific world cheered. Cell-based gene therapies had arrived, offering hope to patients who had run out of options to manage their blood cancers.

CAR T-cell therapy promised to transform cancer treatment; then-FDA Commissioner Scott Gottlieb, MD, heralded “a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer.”6

CONTINUED ON SP85 »
Effective January 1, 2022, report JEMPERLI using the permanent J-CODE J9272
Injection, dostarlimab-gxly, 10 mg*

* J9272 will replace miscellaneous and/or temporary codes that were previously used across various sites of care

* J9272 applies to commercial and Medicare patients in both hospital outpatient and physician's office settings

**INDICATIONS**

JEMPERLI is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced:
- endometrial cancer (EC), as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen, or
- solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

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

**IMPORTANT SAFETY INFORMATION**

**Severe and Fatal Immune-Mediated Adverse Reactions**
- Immune-mediated adverse reactions, which can be severe or fatal, can occur in any organ system or tissue and can occur at any time during or after treatment with a PD-1/PD-L1–blocking antibody, including JEMPERLI.
- Monitor closely for signs and symptoms of immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function tests at baseline and periodically during treatment. For suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.
- Based on the severity of the adverse reaction, withhold or permanently discontinue JEMPERLI. In general, if JEMPERLI requires interruption or discontinuation, administer systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until improvement to ≤Grade 1. Upon improvement to ≤Grade 1, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids.

**Billing Unit Conversion**

<table>
<thead>
<tr>
<th>HCPCS J9272 (Injection, dostarlimab-gxly, 10 mg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
</tr>
<tr>
<td>1 unit</td>
</tr>
<tr>
<td>500-mg vial</td>
</tr>
<tr>
<td>50 units</td>
</tr>
</tbody>
</table>

*Please check with individual payers and carriers for specific documentation and guidance when billing for a new drug. HCPCS=Healthcare Common Procedure Coding System


The decision by a payer to pay for a specific product is based on many factors. It is always the prescriber’s responsibility to determine the appropriate treatment and submit appropriate codes, charges, and modifiers for treatments provided.
**IMPORTANT SAFETY INFORMATION (cont’d)**

**Immune-Mediated Pneumonitis**
- JEMPERLI can cause immune-mediated pneumonitis, which can be fatal. In patients treated with other PD-1/PD-L1–blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Pneumonitis occurred in 1.4% (7/515) of patients, including Grade 2 (1.2%) and Grade 3 (0.2%) pneumonitis.

**Immune-Mediated Colitis**
- Colitis occurred in 1.4% (7/515) of patients, including Grade 2 (0.8%) and Grade 3 (0.6%) adverse reactions. Cytomegalovirus infection/reactivation have occurred in patients with corticosteroid-refractory immune-mediated colitis. In such cases, consider repeating infectious workup to exclude alternative etiologies.

**Immune-Mediated Hepatitis**
- JEMPERLI can cause immune-mediated hepatitis, which can be fatal. Grade 3 hepatitis occurred in 0.2% (1/515) of patients.

**Immune-Mediated Endocrinopathies**
- Adrenal Insufficiency
  - Adrenal insufficiency occurred in 1.4% (7/515) of patients, including Grade 2 (0.8%) and Grade 3 (0.6%). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment per institutional guidelines, including hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.

- Thyroid Disorders
  - Thyroiditis occurred in 0.4% (2/515) of patients; both were Grade 2. Hyperthyroidism occurred in 1.9% (10/515) of patients, including Grade 2 (1.7%) and Grade 3 (0.2%). Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.

- Type 1 Diabetes Mellitus, Which Can Present with Diabetic Ketoacidosis
  - JEMPERLI can cause type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.

**Immune-Mediated Nephritis with Renal Dysfunction**
- JEMPERLI can cause immune-mediated nephritis, which can be fatal. Nephritis occurred in 0.4% (2/515) of patients; both were Grade 2.

**Immune-Mediated Dermatologic Adverse Reactions**
- JEMPERLI can cause immune-mediated rash or dermatitis. Bullous and exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS), have occurred with PD-1/PD-L1–blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue JEMPERLI depending on severity.

**Other Immune-Mediated Adverse Reactions**
- The following clinically significant immune-mediated adverse reactions occurred in <1% of the 515 patients treated with JEMPERLI or were reported with the use of other PD-1/PD-L1–blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.
  - Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nere paresis, autoimmune neuropathy
  - Cardiac/Vascular: Myocarditis, pericarditis, vasculitis
  - Ocular: Uveitis, iritis, other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur
  - Gastrointestinal: Pancreatitis, including increases in serum amylase and lipase levels, gastritis, duodenitis
  - Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica
  - Endocrine: Hypoparathyroidism
  - Other (Hematologic/Immune): Autoimmune hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarciodosis, immune thrombocytopenia, solid organ transplant rejection

**Infusion-Related Reactions**
- Severe or life-threatening infusion-related reactions have been reported with PD-1/PD-L1–blocking antibodies. Severe infusion-related reactions (Grade 3) occurred in 0.2% (1/515) of patients receiving JEMPERLI. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue JEMPERLI based on severity of reaction.

**Complications of Allogeneic HSCT**
- Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after treatment with a PD-1/PD-L1–blocking antibody, which may occur despite intervening therapy. Monitor patients closely for transplant-related complications and intervene promptly.

**Embryo-Fetal Toxicity and Lactation**
- Based on its mechanism of action, JEMPERLI can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after their last dose. Because of the potential for serious adverse reactions from JEMPERLI in a breastfed child, advise women not to breastfeed during treatment with JEMPERLI and for 4 months after their last dose.

**Common Adverse Reactions**
- The most common adverse reactions (≥20%) in patients with dMMR
  - EC were fatigue/asthenia, nausea, diarrhea, anemia, and constipation. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased sodium, decreased leukocytes, decreased albumin, increased creatinine, increased alkaline phosphatase, and increased alanine aminotransferase.

- The most common adverse reactions (≥20%) in patients with dMMR solid tumors were fatigue/asthenia, anemia, diarrhea, and nausea. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased sodium, increased alkaline phosphatase, and decreased albumin.

Please see Brief Summary of full Prescribing Information for JEMPERLI on the following pages.
JEMPERLI (dostarlimab-gxly) injection, for intravenous use

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

1. INDICATIONS AND USAGE
JEMPERLI is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced:

- endometrial cancer (EC), as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen, or
- solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options [see Dosage and Administration (2.1) of full prescribing information]. These indications are approved under accelerated approval based on improved survival, as demonstrated by a significant improvement in overall survival in GARNET. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2. CONTRAINDICATIONS
None.

3. WARNINGS AND PRECAUTIONS
5.1 Severe and Fatal Immune-Mediated Adverse Reactions
JEMPERLI is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or PD-1 ligand (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance, and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed in WARNINGS AND PRECAUTIONS may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which can be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting a PD-1/PD-L1-blocking antibody. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions, such as fever, chills, liver enzymes, creatinine, and thyroid function tests at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialized consultation as appropriate.

Withhold or permanently discontinue JEMPERLI depending on severity [see Dosage and Administration (2.3) of full prescribing information]. In general, if JEMPERLI requires interruption or discontinuation, administer systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic immunosuppressants (e.g., endocrinopathies, dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis
JEMPERLI can cause immune-mediated pneumonitis, which can be fatal. In patients treated with other PD-1/PD-L1-blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-mediated pneumonitis occurred in 1.4% (7/515) of patients receiving JEMPERLI, including Grade 2 (0.2%) and Grade 3 (0.2%) pneumonitis. Pneumonitis led to discontinuation of JEMPERLI in 0.6% patients.

Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 96% of the 7 patients. Two patients reinitiated JEMPERLI after symptom improvement; of these, 1 patient had recurrence of pneumonitis.

Immune-Mediated Colitis
JEMPERLI can cause immune-mediated colitis. Cytoresetalgiusus virus infection/reactivation have occurred in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1-blocking antibodies. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated colitis occurred in 1.4% (7/515) of patients receiving JEMPERLI, including Grade 2 (0.8%) and Grade 3 (0.6%) adverse reactions. Colitis led to discontinuation of JEMPERLI in 1.0% patient.

Systemic corticosteroids were required in 29% (27/7) of patients with colitis. Colitis resolved in 71% of the 7 patients. Of the 3 patients in whom JEMPERLI was withheld for colitis, all reinitiated treatment with JEMPERLI.

Immune-Mediated Hepatitis
JEMPERLI can cause immune-mediated hepatitis, which can be fatal.

Immune-mediated hepatitis occurred in 0.2% (1/515) of patients receiving JEMPERLI, which was Grade 5. Systemic corticosteroids were required and the event resolved.

Immune-Mediated Endocrinopathies
Adrenal Insufficiency: JEMPERLI can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment per institutional guidelines, including hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity [see Dosage and Administration (2.3) of full prescribing information].

Adrenal insufficiency occurred in 1.4% (7/515) patients receiving JEMPERLI, including Grade 2 (0.8%) and Grade 3 (0.6%). Adrenal insufficiency resulted in discontinuation in 1.0% (2/205) patient and resolved in 29% of the 7 patients.

Hyperthyroidism: JEMPERLI can cause immune-mediated hyperplasia. Hyperthyroidism can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hyperthyroidism can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity [see Dosage and Administration (2.3) of full prescribing information].

Hyperthyroidism occurred in 1.4% (7/515) patients receiving JEMPERLI, including Grade 2 (0.8%) and Grade 3 (0.6%). Hyperthyroidism led to discontinuation of JEMPERLI and resolved in 35% of the 7 patients. Systemic corticosteroids were not required for any of the 37 patients with hyperthyroidism.

Type 1 Diabetes Mellitus: Which Can Present with Diabetic Ketoacidosis. JEMPERLI can cause type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity [see Dosage and Administration (2.3) of full prescribing information].

Immune-Mediated Nephritis with Renal Dysfunction
JEMPERLI can cause immune-mediated nephritis, which can be fatal. Nephritis occurred in 0.4% (2/515) of patients receiving JEMPERLI. Of the 2 patients with Grade 2. Nephritis did not lead to discontinuation of JEMPERLI and resolved in both patients. Systemic corticosteroids were required in 1 of the 2 patients experiencing nephritis.

Immune-Mediated Dermatologic Adverse Reactions
JEMPERLI can cause immune-mediated rash or dermatitis. Bullous and exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS), have occurred with PD-1/PD-L1-blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue JEMPERLI depending on severity [see Dosage and Administration (2.3) of full prescribing information].

Other Immune-Mediated Adverse Reactions
The following clinically significant immune-mediated adverse reactions occurred in <1% of the 515 patients treated with JEMPERLI and are reported with the use of other PD-1/PD-L1-blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions:

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome, myasthenia gravis, Guillain-Barre syndrome, neuro paralytic, autoimmune neuropathy.

Cardiovascular: Myocarditis, pericarditis, vasculitis.

Endocrine: Hypothyroidism. Other (Hematologic/Immunologic): Autoimmune hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Rikuchi lymphadenopathy), sarcoidosis, immune thrombocytopenia, solid organ transplant rejection.

5.2 Infusion-Related Reactions
Severe or life-threatening infusion-related reactions have been reported with PD-1/PD-L1-blocking antibodies. Severe infusion-related reactions (grade 3) occurred in 0.2% (1/515) of patients receiving JEMPERLI. All patients recovered from the infusion-related reactions.

Monitor patients for signs and symptoms of infusion-related reactions. For Grade 2 or higher infusion-related reactions, withhold or permanently discontinue JEMPERLI based on severity of reaction [see Dosage and Administration (2.3) of full prescribing information].

5.3 Complications of Allogeneic HSCT
Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1-blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD,

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

5.3 Complications of Allogeneic HSCT
Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1-blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD,
5.3 Complications of Allogeneic HSCT (cont)

chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-resistant febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1–blocking antibody prior to or after an allogeneic HSCT.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, JEMPERLI can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus, resulting in fetal death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after the last dose (see Use In Specific Populations (8.1, 8.3)).

6 ADVERSE REACTIONS

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

• Severe and fatal immune-mediated adverse reactions (see Warnings and Precautions (5.1))
• Infusion-related reactions (see Warnings and Precautions (5.2))

6.1 Clinical Trials Experience

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

The pooled safety population described in WARNINGS AND PRECAUTIONS reflects exposure to JEMPERLI as a single-agent in 515 patients with advanced or recurrent solid tumors in the nonrandomized, open-label multicohort GARNET trial that enrolled 290 patients with endometrial cancer and 225 patients with other solid tumors. JEMPERLI was administered intravenously at doses of 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks until disease progression or unacceptable toxicity. Among the 515 patients, 42% were exposed for ≥24 weeks and 26% were exposed for >48 weeks.

Mismatch Repair Deficient (dMMR) Endometrial Cancer

The safety of JEMPERLI was evaluated in GARNET in 104 patients with advanced or recurrent dMMR EC who received at least 1 dose of JEMPERLI (see Clinical Studies (4.4) for full prescribing information). Patients received JEMPERLI 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks as an intravenous infusion until disease progression or unacceptable toxicity. Among the 515 patients, 42% were exposed for ≥24 weeks and 26% were exposed for >48 weeks.

Serious adverse reactions occurred in 34% of patients receiving JEMPERLI. Serious adverse reactions in ≥2% of patients included sepsis (2.9%), acute kidney injury (2.9%), urinary tract infection (2.9%), abdominal pain (2.9%), and pyrexia (2.9%).

JEMPERLI was permanently discontinued due to adverse reactions in 5 (4.8%) patients, including increased transaminases, sepsis, bronchitis, and pneumonitis. Dose interruptions due to adverse reactions occurred in 23% of patients who received JEMPERLI. JEMPERLI 47% were exposed for 6 months or longer and 20% were exposed for >1 year.

Table 2. Adverse Reactions (≥10%) in Patients with dMMR Endometrial Cancer Who Received JEMPERLI in GARNET

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General and administration</td>
<td>48</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea</td>
<td>30</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26</td>
<td>1.9</td>
</tr>
<tr>
<td>Constipation</td>
<td>20</td>
<td>0.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Blood and lymphatic system</td>
<td>Anemia</td>
<td>24</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>Decreased appetite</td>
<td>14</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal</td>
<td>Cough</td>
<td>14</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>Pruritus</td>
<td>14</td>
</tr>
<tr>
<td>Infec tions</td>
<td>Urinary tract infection</td>
<td>13</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td>Myalgia</td>
<td>12</td>
</tr>
</tbody>
</table>

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

Table 3. Laboratory Abnormalities that Worsened from Baseline to Grade 3 or 4 in ≥1% of Patients with dMMR Endometrial Cancer Receiving JEMPERLI in GARNET

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>JEMPERLI N = 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td>All Grades</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>37</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>27</td>
</tr>
<tr>
<td>Chemistry</td>
<td>Decreased albumin</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>27</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>25</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>16</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>15</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Decreased sodium</td>
</tr>
<tr>
<td>Increased calcium</td>
<td>15</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>15</td>
</tr>
</tbody>
</table>

Increased transaminases include alanine transaminase, aspartate transaminase, and total bilirubin.

Table 4. Adverse Reactions (≥10%) in Patients with dMMR Recurrent or Advanced Solid Tumors in GARNET

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General and administration</td>
<td>Fatigue</td>
<td>42</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Blood and lymphatic system</td>
<td>Anemia</td>
<td>30</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea</td>
<td>25</td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>0.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>1.3</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>0.4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>Pruritus</td>
<td>15</td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>0.4</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal</td>
<td>Cough</td>
<td>13</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>Decreased appetite</td>
<td>12</td>
</tr>
</tbody>
</table>

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

Table 5. Laboratory Abnormalities that Worsened from Baseline to Grade 3 or 4 in ≥1% of Patients with dMMR Endometrial Cancer Receiving JEMPERLI in GARNET

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>JEMPERLI N = 267</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td>All Grades</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>37</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>27</td>
</tr>
<tr>
<td>Chemistry</td>
<td>Decreased albumin</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>27</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>25</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>16</td>
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<tr>
<td>Increased alanine aminotransferase</td>
<td>15</td>
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<tr>
<td>Electrolytes</td>
<td>Decreased sodium</td>
</tr>
<tr>
<td>Increased calcium</td>
<td>15</td>
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<tr>
<td>Decreased potassium</td>
<td>15</td>
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Increased transaminases include alanine transaminase, aspartate transaminase, and total bilirubin.

Mismatch Repair Deficient or Recurrent or Advanced Solid Tumors

The safety of JEMPERLI was investigated in 267 patients with recurrent or advanced dMMR solid tumors enrolled in GARNET (see Clinical Studies (4.2) of full prescribing information). Patients received JEMPERLI 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks as an intravenous infusion until disease progression or unacceptable toxicity. Among the 267 patients, 42% were exposed for≥24 weeks and 26% were exposed for >2 years of treatment or a medical condition that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Among patients receiving JEMPERLI, 47% were exposed for 6 months or longer and 20% were exposed for >1 year.

Serious adverse reactions occurred in 34% of patients receiving JEMPERLI. Serious adverse reactions in ≥2% of patients included sepsis (2.9%), acute kidney injury (2.9%), urinary tract infection (2.9%), abdominal pain (2.9%), and pyrexia (2.9%).

JEMPERLI was permanently discontinued due to adverse reactions in 5 (4.8%) patients, including increased transaminases, sepsis, bronchitis, and pneumonitis. Dose interruptions due to adverse reactions occurred in 23% of patients who received JEMPERLI. JEMPERLI 47% were exposed for 6 months or longer and 20% were exposed for >1 year.

Table 2 summarizes the adverse reactions that occurred in ≥10% of patients with dMMR EC on JEMPERLI in GARNET.

Table 3 summarizes laboratory abnormalities worsening from baseline to Grade 3 or 4 in ≥1% of patients with dMMR EC on JEMPERLI in GARNET.

Table 4 summarizes the adverse reactions that occurred in ≥10% of patients with dMMR solid tumors on JEMPERLI in GARNET.
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, JEMPERLI can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology (12.1) for full prescribing information). There are no available data on the use of JEMPERLI in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death (see Data). Human IgG4 immunoglobulins (IgG4) are known to cross the placental barrier; therefore, dostarlimab-gxly has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

8.2 Lactation

Risk Summary

There is no information regarding the presence of dostarlimab-gxly in human milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment and for 4 months after the last dose of JEMPERLI.

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating JEMPERLI (see Use in Specific Populations (8.1)).

Contraception

Females: Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after the last dose.

8.4 Pediatric Use

The safety and efficacy of JEMPERLI have not been established in pediatric patients.

8.5 Geriatric Use

Of the 515 patients treated with JEMPERLI, 51% were younger than 65 years, 37% were aged 65 through 75 years, and 12% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

17 PATIENT COUNSELING INFORMATION

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

Immune-Mediated Adverse Reactions

Advise patients to contact their healthcare provider immediately for severe or worsening symptoms of infusion reactions (see Warnings and Precautions (5.5)).

Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for severe symptoms of infusion reactions (see Warnings and Precautions (5.5)).

• Atelectasis: Advise patients to contact their healthcare provider immediately for severe or worsening symptoms of atelectasis, pneumonia, or interstitial lung disease (see Warnings and Precautions (5.4)).

• Severe skin reactions: Advise patients to contact their healthcare provider immediately for severe symptoms of skin reactions, SJS, TEN, or DRESS (see Warnings and Precautions (5.5)).

• Other immune-mediated adverse reactions:

Infusion-Related Reactions

• Pneumonitis: Advise patients to contact their healthcare provider immediately for severe or worsening cough, chest pain, or shortness of breath (see Warnings and Precautions (5.1)).

• Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain (see Warnings and Precautions (5.1)).

• Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding (see Warnings and Precautions (5.5)).

• Immune-mediated endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, nephritis, adrenal insufficiency, hypophysitis, or type 1 diabetes mellitus (see Warnings and Precautions (5.5)).

• Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis (see Warnings and Precautions (5.5)).

8.6 Animal Data

There are no available data on the use of JEMPERLI in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death (see Data).

In the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to dostarlimab-gxly may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.8 Pregnancy

Verify pregnancy status in females of reproductive potential prior to initiating JEMPERLI (see Use in Specific Populations (8.1)).

8.9 Lactation

Advise women not to breastfeed during treatment with JEMPERLI and for 4 months after the last dose (see Use in Specific Populations (8.2)).

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FROM THE PUBLISHER

In Oncology Payment Reform, Answers Are Not Too Much to Ask

ONCOLOGY PAYMENT REFORM has moved beyond the experimental phase. If anything, the reformers at the Center for Medicare & Medicaid Innovation (CMMI) did their job so well that many concepts have taken hold in the commercial sector. Reform is moving ahead, with or without the government.

But Medicare’s footprint in oncology care is too large to ignore, so CMMI’s decision to let the Oncology Care Model (OCM) wrap up on June 30—with no replacement in sight—has community practices scratching their collective heads. Practices that spent more than 5 years investing in payment reform will lose funds that helped improve the quality of care delivery for thousands of patients. Some smaller practices may be forced to eliminate care navigators or other staff who helped patients schedule appointments, develop survivorship plans, ensure good nutrition, or stay out of the emergency department on the weekends.

What’s more, the OCM allowed practices to fulfill elements of a 2015 law that required participation in payment reform. So must oncologists now spend more money to ramp up for a different model or system?

Practices have asked CMS leadership for nearly a year what to expect and have heard almost nothing. The Community Oncology Alliance (COA) has called on CMMI to give practices guidance or extend the OCM until a replacement is created, lest the investment made since 2016 be wasted. In this issue of Evidence-Based Oncology™ (EBO), we report on a COA survey that found the OCM features that did the most to help patients will be at risk if the model ends abruptly.

One criticism of early CMMI models is that they failed to address health equity. This is a fair point, and COA President Kashyap Patel, MD, who is the associate editor of EBO, has wholeheartedly endorsed efforts to reduce cancer care disparities in a future model. But that will be hard to do if the infrastructure that made patients’ lives better under the current OCM is dismantled before a new model is released.

Change is not easy. It’s understandable that a new team at CMMI may wish to reexamine a 5-year-old model with a fresh lens. However, it’s not acceptable to shut out leaders of the oncology community who undertook payment reform in good faith—including those who put their practices at financial risk.

If payment reform in cancer care is about accountability, both sides must be accountable.

Sincerely,
Mike Hennessy Jr
President & CEO

FROM THE PUBLISHER

In Oncology Payment Reform, Answers Are Not Too Much to Ask

FROM THE EDITOR IN CHIEF

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JOSEPH ALVARNAS, MD

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A survey by the Community Oncology Alliance found that enhanced services under the Oncology Care Model, such as navigators who assist patients through the care journey, could be lost at some practices without funds to support the positions.

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From the Earth to the Moon (and Back)

ON FEBRUARY 2, President Joseph R. Biden Jr. announced the next arc of the Cancer Moonshot initiative and emphasized key deliverables in the battle against cancer. He noted that advances in cancer care, including those in genomics, immuno-oncology, and targeted therapeutics, had resulted in a 25% reduction in cancer mortality over the past 25 years. Goals of the reinvented Cancer Moonshot include accelerated and broader deployment of screening, a renewed focus on improving the equity of care delivery and survival outcomes, and a reorganization of key governmental leaders to speed up success. The president’s aim is a 50% reduction in age-adjusted cancer deaths by 2047.1,2 These goals seem audacious, but they are likely achievable. The importance of early and effective systems for cancer screening cannot be overstated. The COVID-19 pandemic has exacerbated the issue of access to screening in unprecedented ways. Data from an Epic system analysis show that “screening appointments for breast, cervical, and colon cancers in March 2020 decreased between 86% and 94% compared with average volumes in the prior 3 years.”3 The administration’s push on improving screening rates, especially in underserved communities, is likely to produce an outsized impact on cancer survival rates over the next 2 decades.

Reinforcing our new therapeutic pipeline is also an essential component of ensuring the Moonshot’s success. Data show that some of the greatest recent improvements in cancer survival have occurred in cancer types that respond to advanced care technologies. Increasing the depth and diversity of our anticancer portfolio will empower countless cures and extraordinary progress in improving quality of life for patients with cancer.

In this issue of Evidence-Based Oncology4, we examine some of these new care technologies and their evolving role in improving outcomes. Mary Caffrey reviews the implications of the approval of chimeric antigen receptor T-cells as second-line treatment for relapsed and refractory aggressive non-Hodgkin lymphoma. In our interview with Nicholas McAndrew, MD, MSCE, a medical oncologist and breast cancer specialist at UCLH Health, we evaluate the use of CDK4/6 inhibitors in metastatic HR+/HER2-negative breast cancer. Beyond technology, however, we cannot get onto a path toward better, more equitable care without creating systems that can deliver that care in more sustainable, patient-centered ways. In this issue, Stephen Schleicher, MD, MBA, discusses his new role at Tennessee Oncology that will focus on building systems of care that integrate palliative care and genetics counseling into a more patient-centered model. We also focus upon how to leverage models of telehealth to ensure continuity of cancer care in an era of COVID-19–related disruptions.

I believe that we are at the brink of realizing the promise of the Moonshot. That realization, however, will require that we bring our efforts down to earth. Discovery alone cannot ensure care equity absent ensuring that all patients, including the under-served, benefit from these advances. Ultimately, we cannot technologize our way to lower cancer mortality rates. We must ground these advances in the reality of the human experience. President Biden noted that, “Despite all the progress, there’s still a sense of powerlessness, guilt, and fear.”4 Our systems and aspirations must ensure that the vulnerable person whom we are privileged to treat is at the center of our innovation and systems building. That is a challenge that lies here, back on earth: The place where lofty aspirations and high rhetoric must ultimately land if it is to succeed.

Joseph Alvarnas, MD
Editor-in-Chief

REFERENCES

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Steven Pergam, MD, MPH, Discusses NCCN’s “Strong Preference” for mRNA Vaccines in Patients With Cancer to Prevent COVID-19

Mary Caffrey

The National Comprehensive Cancer Network (NCCN) announced significant updates to its expert consensus recommendations on vaccination and prevention of COVID-19 in people with cancer on January 4, listing a preference for mRNA-based vaccines and calling for patients and caregivers alike to receive boosters.1

A statement from NCCN’s Advisory Committee on COVID-19 Vaccination and Pre-exposure Prophylaxis said that the panel “endorses vaccination for all eligible persons based on FDA-approved indications or emergency use authorization” and emphasized the need for everyone to be fully vaccinated—including third doses.

Caregivers and close contacts of persons with cancer should also be fully vaccinated to offer the best possible protection for those who are immunocompromised, the experts recommend. The recommendations call for vaccination among the general public.

“Patients are a little more protected than they were in the initial phase of the pandemic. I think people are also being more cautious....They know to wear masks in public; they’re more cautious about going out in group activities. I think our cancer patients are more aware, as our providers are about providing that advice.”

—Steven Pergam, MD, MPH, director of infection prevention, Seattle Cancer Care Alliance; infectious disease physician, Fred Hutchinson Cancer Research Center

Vaccination should be delayed for at least 3 months following hematopoietic cell transplantation or engineered cellular therapy, such as chimeric antigen receptor (CAR) T-cell therapy, to ensure the best possible vaccine efficacy. These are the same recommendations given to the public who have been exposed to COVID-19 or have received recent monoclonal antibody therapy.

While the committee supports any of the possible FDA-approved vaccines, it expressed “strong preference” for the mRNA vaccines—Pfizer/BioNTech, which has full FDA approval in adults, or Moderna.

The committee also “strongly supports mandates for health care worker vaccination.”

“All of us are called to do everything we can to save as many lives as possible during the ongoing pandemic,” Robert W. Carlson, MD, chief executive officer, NCCN, said in a statement.2

“Vaccination is our most effective approach for avoiding serious COVID-19 complications, including hospitalization and death. However, research shows many immunocompromised people develop inadequate immune responses from vaccines,” Carlson said. “Thankfully, we now have additional tools to help people in active treatment for cancer, solid organ transplant recipients, engineered cellular therapy (eg, CAR T-cell) or stem cell transplant recipients (also called hematopoietic stem cells), and those with other immunodeficiency-causing conditions (such as HIV, DiGeorge syndrome, or Wiskott-Aldrich syndrome).”3

“We have new agents to prevent and treat COVID-19 that will benefit patients with cancer,” said Bramh Segal, MD, of Roswell Park Comprehensive Cancer Center, a co-leader of the NCCN Advisory Committee on COVID-19 Vaccination and Pre-exposure Prophylaxis. “An important challenge on a national level is to ensure drug availability to patients with cancer and others at high risk for COVID-19. The revised recommendations from the NCCN Advisory Committee on COVID-19 Vaccination and Pre-exposure Prophylaxis will provide guidance on the use of these agents for patients with cancer, including prioritization when supplies are limited.”

In its statement, the committee said it also supports recommendations from the CDC, the American Society of Transplantation and Cellular Therapy, and the American Society of Hematology (ASH) that previously vaccinated patients completing stem cell transplantation or engineered cellular therapy should receive a repeat vaccination series starting at 3 months post treatment.

Steven Pergam, MD, MPH, director of infection prevention at Seattle Cancer Care Alliance and infectious disease physician at Fred Hutchinson Cancer Research Center, serves as a co-leader for the NCCN Advisory Committee on Covid-19 Vaccination and Pre-exposure Prophylaxis. Pergam spoke with Evidence-Based Oncology® (EBO) on the day the update was released about the evolution of NCCN’s recommendations and key takeaways from the update.

EBO: What are the most important takeaways from NCCN’s update on COVID-19 vaccines and prevention?

PERGAM: Things change quite a bit, and we hadn’t had an update in a little while. [We] specifically addressed some of the vaccine changes that have come along in the past few months. One is a recommendation for an additional booster after the Johnson & Johnson vaccine. We made some updates specifically to address that. We also addressed some questions around antibody testing, and whether to test patients for antibodies who are going through the vaccine process. We updated the new recommendations for children to get vaccinated in the lower age ranges. We [also] discussed [the] important [issue of the] mix-and-match approach that was approved by the FDA and others, where you don’t necessarily have to get the same vaccine [for a booster]. We really were encouraging people to make sure that they’re getting vaccinated and, if they had received the Johnson & Johnson or Pfizer, that it was possible to get [a different] vaccine to complete your series.

Finally, the biggest news [from the CDC] was that the mRNA vaccines are the primary selection, and that’s primarily what we’re recommending as the first choice if possible. The new addition was related to monoclonal antibody prevention, which is a new drug called Evusheld, made by AstraZeneca. It’s a prophylaxis agent, so it’s given for preexposure prophylaxis in high-risk immunosuppressed patients. That’s a drug that’s like other monoclonals that have been given for treatment, but instead, it has a longer half-life—at least it’s reported to have a longer half-life. Patients who might not respond as well to vaccines [can get this] and are
probably more protected against COVID-19 during that period after dosing. We made some specific recommendations about groups who should be targeted for that particular therapy, and that’s consistent with the [National Institutes of Health] guidelines that were recently published.

EBO: From your vantage point in Seattle, you have seen the trajectory of COVID-19 and cancer from the very start of the pandemic. Have any major recommendations evolved or shifted since the beginning?

PERGAM: Being on the forefront of this was kind of challenging at the beginning, I think what you’ve seen is that people really work together to try to protect patients as best as possible. We’ve gone from little masking in the community to masking in the community and masking in health care institutions. We’ve seen a shift from having no therapies available to now therapies being available. We’ve had a shift from no vaccines to vaccines. I think the biggest shift right now is just the number of people who are getting infected; Omicron’s ability to transmit is quite a big shift.

Despite being engaged in this very early, I think we [are nonetheless surprised at] the number of patients who we’re seeing who are coming up positive now, just because it’s so much more prevalent. We are in a different situation, though, because we do have some treatments available, and we have people who are vaccinated. So, I think in general, patients are a little more protected than they were during the initial phase [of the pandemic]. I think people are also being more cautious. I think they’ve learned a lot through the process: They know to wear masks in public; they’re more cautious when they go out in group activities. I think our cancer patients are more aware, as are our providers about providing that advice.

EBO: Just before the Pfizer vaccine received its Emergency Use Authorization, the director of the National Institute of Allergy and Infectious Diseases, Anthony Fauci, MD, recommended at the American Society of Hematology meeting in December 2020 that patients with blood cancers get vaccinated. He said that even if the vaccine was not fully effective, some protection was better than none. Is that advice still basically true?

PERGAM: Understanding exactly how vaccines work in an immunosuppressed population, [with] cancer patients being one of those, is still really complex. We know that we use antibody levels and antibody responses to vaccine as a surrogate marker for protection. But other aspects of the immune system are harder to assess—things like T-cell immunity—that also probably play important roles, so even people who don’t have full antibody responses may have some level of protection. [As] I try to explain to patients, you don’t want to meet COVID on the street unless you’ve been vaccinated first, because that’s going to give you some protection. Even if it’s a small percent—if it gives you protection of, say, 10%—it’s better than going into that meeting not protected at all. So, vaccines are important. What has shifted is now we’re doing more aggressive vaccines. Instead of doing 2 doses, we’re doing 3 doses as the primary, with a boost about 6 months later. I think that boost is important and can provide additional protection. Immunosuppressed patients have a lot of opportunities to get additional benefits from vaccines. They’re not perfect, and you still need to think about other things that you can do to protect yourself, but I absolutely agree that vaccine remains the most important prevention method we have as a primary, and then those others are just as critical—the masking, social distancing, etc.

EBO: The NCCN preference for mRNA vaccines aligns with data presented in December 2021 by the Leukemia and Lymphoma Society at the ASH meeting in Atlanta. Can you discuss why the mRNA vaccines offer better protection for these patients?

PERGAM: I can’t speak to why it’s better. [There are always] nuances of how these vaccines work and the specifics about [how they work in] particular populations, and the [mRNA vaccine], this particular approach, does seem to be a particularly powerful method for delivering [protection against] COVID. [This is] how it works basically: These are coated in a lipid particle with an mRNA component in it that basically connects and goes into a cell. The mRNA goes into the cell; the mRNA then transcribes the mRNA components and makes it into a protein production in the cell, and that protein is the spike protein that’s put onto the surface of the cell. It doesn’t actually cause infection… but it allows the immune system to create a response to that spike protein, and that has the ability to create an immune response, which is what we need to be prepared for the next time it sees that.

The way it’s been described by some people, it’s like a “Wanted” poster: It’s there, you see it, and then it disappears, but everyone remembers what was on that poster. On that spike protein, that immune system is now ready for that individual when it comes through.

The adenosine vectors are a little bit different. They use a similar process to get information in, but a viral vector uses that same mechanism instead of doing it through that lipid particle. They’re a little bit different in how they work. It’s unclear exactly—I can’t speak to why one is necessarily better than the other—but definitely the mRNA vaccines appear to have a more robust immune response, at least by antibody levels, particularly, within the immunosuppressive population. Now, there may be some advantages to adenosine vaccines—there may be some more longer-term T-cell responses—but I think we’re going to need to continue to study this and understand how they each work and where specific niches may work better than others.

EBO: Can you discuss the NCCN recommendations for patients receiving CAR T-cell therapy?

PERGAM: If people are getting CAR T-cell therapy or [bone marrow transplant] therapy, you’re sort of replacing or really updating their immune system; so, even if they’ve been previously vaccinated with a full series, they need to be revaccinated post procedure. [In other words], with an allogeneic transplant, you’re providing a whole new immune system, and a lot of those [previous] memory cells are gone; therefore, you need to reeducate the system… We’re revaccinating all those patients post those events because of the way the therapy affects the immune system in general, and that has been a big update. I think, in this time frame. We’re waiting typically about 3 months post therapy, because we want that cellular recovery to be back and then vaccinate them at that time.

REFERENCES

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FCS’ Bailey Discusses 4-Drug Regimens, Use of MRD in Multiple Myeloma

RAY BAILEY, BPHARM, RPH, is the senior vice president of pharmacy services for Florida Cancer Specialists (FCS) Pharmacy Services operations. In this role, Bailey oversees intravenous and oral medications and is responsible for financial management, business development, new drug access, purchasing contracts, and overall formulary management. Bailey joined FCS in 2008 as pharmacy manager and was later promoted to director of pharmacy for the FCS Oral Oncolytic Pharmacy (Rx to Go). Bailey spoke with Evidence-Based Oncology™ (EBO) just after the conclusion of the 63rd American Society of Hematology (ASH) Meeting & Exposition, which took place December 11-14, 2021. This interview was edited lightly for clarity.

EBO: Could you describe the health care resource utilization of a patient with multiple myeloma. What are the drivers of costs for this disease state?

BAILEY: It’s the drugs, for sure. Pretty much for all the patients, whether they’re transplant eligible or not, when you get into relapsed/refractory disease, they’re going to be on triplet or quadruplet therapies now—so a lot of cost in the drugs.

As I review this, there’s not a lot of opportunities [for savings]. Looking at overall cost, there’s not much of a difference between the regimens in myeloma therapy. So absolutely, drug costs drive multiple myeloma [resource utilization] in our practice.

EBO: How does the economic burden change as patients start progressing toward that relapsing/remitting multiple myeloma stage, as opposed to the initial onset of the disease?

BAILEY: It depends on whether the patients are transplant eligible or transplant ineligible. A lot of these patients are seeing anti-CD38 [therapy] early, in the front line. So when they progress, they may see it anti-CD38 again, or not. We’re currently looking at our formulary pathways in that space and trying to define and tease out what comes post anti-CD38. But the other therapies are as expensive or more expensive; these are usually more novel, newer drugs [and] can be more costly.

The patients are going to be heavily pretreated. They’ll move down through the different lines of therapy; now we’ve got anti-BCMA CAR T [immunotherapy]. We’ll have bispecific [antibodies] next year, probably. So, I would expect [for] those patients, as they live longer, [that] those costs the will continue to escalate.

EBO: How would you say that the cost of multiple myeloma compares with other oncology priorities that you’re treating, such as breast cancer, for example?

BAILEY: I don’t think we’ve defined per se, by disease state, which is the biggest driver. We are a value-based organization; probably 70% of our patients are in the value-based OCM [Oncology Care Model]. We’re not sure what’s going to happen next year with the OCM. But from our OCM data, it looks like multiple myeloma is one of our biggest drivers of cost. I can’t say for sure that it’s the biggest driver, because you’re right—there’s a lot of innovation, a lot of disease states with a lot of expensive therapies—but probably multiple myeloma would be at the top or top 3, for sure.

EBO: Given that cost, what is your strategy for evaluating treatments for value? How do you gain value out of what’s coming down the pipeline in multiple myeloma and what’s currently being used to treat these patients?

BAILEY: So, we’re a NCCN [National Comprehensive Cancer Network] practice; we follow NCCN guidelines. As I mentioned it earlier, we have a formulary navigator pathway [in which] we look at each individual’s disease state and we try to assign value to individual regimens where there may be multiple choices. We’ll crunch the numbers on the total cost and compare that to the NCCN category, and then we may have a preferred regimen in a specific line of therapy by disease state, or a couple that we’ve identified as preferred based on the way we look at it through our [pharmacy and therapeutics committee], which is efficacy first, side effect profile, and then value.

“We have developed what I think is a very innovative tool. It’s a proprietary tool—we call it a formulary navigator—where we put an incredible amount of work into looking at all the disease states, and then creating based on line of therapy—specific regimens for our practitioners, with [the National Comprehensive Cancer Network guidelines] as the backbone.”

—Ray Bailey, BPharm, RPh, senior vice president, pharmacy services, Florida Cancer Specialists Pharmacy Services

EBO: Given the economic burden, what is the health care resource utilization of a patient with multiple myeloma, and what are the drivers of costs for this disease state?

BAILEY: So, we’re a NCCN [National Comprehensive Cancer Network] practice; we follow NCCN guidelines. As I mentioned it earlier, we have a formulary navigator pathway [in which] we look at each individual’s disease state and we try to assign value to individual regimens where there may be multiple choices. We’ll crunch the numbers on the total cost and compare that to the NCCN category, and then we may have a preferred regimen in a specific line of therapy by disease state, or a couple that we’ve identified as preferred based on the way we look at it through our [pharmacy and therapeutics committee], which is efficacy first, side effect profile, and then value.

“We have developed what I think is a very innovative tool. It’s a proprietary tool—we call it a formulary navigator—where we put an incredible amount of work into looking at all the disease states, and then creating based on line of therapy—specific regimens for our practitioners, with [the National Comprehensive Cancer Network guidelines] as the backbone.”

—Ray Bailey, BPharm, RPh, senior vice president, pharmacy services, Florida Cancer Specialists Pharmacy Services

We try to assign a value to that specific regimen. It [involves] a lot of different things. First, for the total cost of care: We are value based, [so] we’re looking at what is that cost for that line of therapy. And we’re looking at other things that create value for the practice as well. Those all come into play on that third component, which is third after efficacy and side effect profile.

And then, obviously, our doctors are free to choose whatever they think is best for that individual patient. If you’re looking at something like multiple myeloma, that’s going to include [whether the patient is] high risk, cytogenetics, comorbidities—things like that come into play. You can’t specifically say “Well, you should use this regime,” because every patient should be individualized. And that’s what our doctors do.

EBO: Keeping that in mind, are there specific clinical outcomes, such as efficacy or the safety profile or overall survival rates, that are impressive, that demonstrate high value? And are there nonclinical outcomes, such as whether a drug is competitive on
cost or participation in a value-based agreement, that you find to be of high value personally when you’re evaluating these drugs?

**BAILEY:** Multiple myeloma is very complex. I can say in other disease states, it’s a lot easier to do this. If you look at all the different oncology disease states, when we’re applying value-based metrics and parameters to it, it can be very easy, kind of cut-and-dry. But with multiple myeloma, it’s very tough to do.

We’re seeing that perhaps there’ll be some opportunities for generics, where we could assign some value there. Bortezomib has been off patent for a while, but we can’t use it sub-Q [in a subcutaneous] formulation. So we’re going to have an opportunity with a sub-Q generic version of bortezomib in probably April or May of (2022). That will help us assign some value. Then, I think lenalidomide is supposed to be available as a generic in the first quarter of (2022). However, because of the complex REMS [Risk Evaluation and Mitigation Strategy], it looks like it’s just going to be a small percentage of the total amount. So there may be some opportunities for lenalidomide generics to create some value there.

**EBO:** You mentioned formulary pathways previously. And I’d like to speak more about that. How are you using clinical pathways, formulary navigators, and clinical decision support tools to support selection of some of these therapies that we mentioned? Are these therapies that we know gain value for patients—that have great efficacy, safety profiles, and good outcomes as a result?

**BAILEY:** We haven’t gone the way of pathways yet. We have developed what I think is a very innovative tool. It’s a proprietary tool—I call it formulary navigator—where we put an incredible amount of work into looking at all the disease states, and then creating based on line of therapy—specific regimens for our practitioners, with [National Comprehensive Cancer Network guidelines] NCCN as the backbone. And by line of therapy. Once we built that, we have a team of clinical BCOPs [Board Certified Oncology Pharmacists] that manages that whole catalog of different disease states and decision support tools that we put in. We update it, because the NCCN is changing constantly, as you know.

What we do is we commit to our practitioners that we will change it at least monthly. If some practice—changing data come out, we may update our formulary navigator more often, but we’ve committed to at least monthly changes [based on] NCCN in our formulary navigator, which is a lot of work. Some people may not realize how much energy and effort it takes to just keep up with NCCN.

**EBO:** I think you made a great point. I think I was looking for some updated guidelines just recently, and it looks like the NCCN is posting nonstop on some of these cancer oncology disease states. But with that in mind, how are you using these tools specifically for the anti-CD38 therapies for multiple myeloma?

**BAILEY:** As I mentioned it earlier, we’re seeing a lot of [daratumumab] for nontransplant-eligible patients, front line. So those regimens are very prominent. And I think there’s a lot of uptake inside of our practice, particularly, for nontransplant-eligible patients, for sure. But they’re probably highlighted more in the relapsed/refractory section of our formulary navigator for multiple myeloma.

I guess the big question out there is sequencing between the 2 anti-CD38 therapies that are there. I guess there is some data to support sequencing the anti-CD38 after a 6-month period. I don’t typically make those kinds of judgments for our patients, but I do know, there’s evidence there. We are currently in the process of defining in that relapse/refractory section, post–anti-CD38, and trying to define and tease out regimens to use post–anti-CD38. I think that will be valuable. But that’s because the NCCN gets very complex and convoluted when you’re looking at relapsed/refractory. And if we can do anything to guide our physicians there or provide them with some decision support tool, we want to do that for them.

**EBO:** You make a great point, that the NCCN guidelines end up reading a bit like a huge tree, rather than a straight line for a physician. So anything to guide them is very valuable. I think you mentioned previously the use of anti-CD38 therapies up front, then in newly diagnosed multiple myeloma, using something like an anti-CD38 plus IVId [lenalidomide, bortezomib, dexamethasone] combination. There are 2 of them—that daratumumab and ixazotumab. Both had some recent trial data in this patient population. How do you evaluate value of a 4-drug regimen? What goes through your mind when considering who should be taking a 4-drug regimen? Or are you still waiting for more data to better support their use?

**BAILEY:** There was a lot at ASH specifically around using the 4-drug regimens for induction transplant consolidation. I think 2 that you referenced had 24-month maintenance with MRD [minimal residual disease] surveillance. So that’s amazing. I hope that takes hold; of course, it’s going to have to make its way into the NCCN guidelines. I think that we already have 4-drug regimens in our formulary navigator for transplant-eligible, high-risk patients. I think that’s [level] 2A NCCN now, so it’s there. But this whole novel idea of fixed duration maintenance afterward with MRD surveillance—I think is fascinating. And I hope I hope that the data bear out.

**EBO:** I think the use of MRD and multiple myeloma is particularly innovative. Both trials I mentioned were using MRD negativity to measure their outcomes. Can you speak some more about this? How does your practice use MRD? What do you think of this outcome? What does it mean for patients, for physicians, and for oncology practices?

**BAILEY:** As I said, I don’t make clinical decisions, but I’m around oncology a lot. I think even if you talk to multiple myeloma experts, they don’t always have the same opinion on using MRD. And I think it’s probably the same case with our physicians. We do use it, it’s available, they can order it. You know, I think it applies also to the [chronic lymphocytic leukemia] space. We put footnotes in our formulary navigator for multiple myeloma in CLL, considering MRD testing, so I don’t think it’s taken hold yet, but it’s there. And if some of the data from ASH pan out, then I think we’re going to see more of it for surveillance after a fixed-duration maintenance. Then it could make sense, particularly for lower-risk, or for patients with 1 risk factor.

**EBO:** It’s an area of innovation. I’ve seen some studies that involve sparing maintenance in patients based on MRD negativity. I think some institutions in the United States are using it that way. Are any other ways that MRD might be being used to advance our cancer care, whether it be multiple myeloma, or, as you mentioned, CLL?

**BAILEY:** I’ve seen some pilots from payers around the country where they’re keenly focused on MRD testing. And they’re doing pilots as a value-based option for practices that want to participate, where they’re looking at doing MRD surveillance; fixed-duration maintenance is where there could be cost savings to the system. And there could be value there. I know we’re going to see more of it the future. I just don’t think it’s prime time yet, so to speak.

**EBO:** Is there anything else you’d like to add?

**BAILEY:** Along the theme of MRD, I think this is fascinating in that right now, these patients are on long periods of maintenance with lenalidomide or high-risk patients are on bortezomib-lenalidomide. We have our own internal specialty pharmacy to manage the business of patients on lenalidomide long-term maintenance. It’s not always an easy drug for patients to take, and it’s very costly. So that maintenance phase can be very costly. More importantly, the patients would love to have a holiday and have something fixed duration—I see that now in CLL. Now, I think our doctors are starting to see the opportunity of fixed duration for first- and second-line treatment of CLL. I’d love to see it in multiple myeloma; I’d love to give patients a drug holiday. So hopefully that data will pan out, and we can have fixed-duration maintenance for multiple myeloma.
No Reason Not to Start With CDK4/6 Inhibitors in Metastatic HR+, HER2-Negative Breast Cancer, McAndrew Says

EVIDENCE-BASED ONCOLOGY (EBO) recently spoke with Nicholas McAndrew, MD, MSCE, an assistant clinical professor of medicine at the University of California, Los Angeles (UCLA) in the Division of Hematology/Oncology and a medical oncologist and breast cancer specialist at UCLA Health. EBO asked McAndrew about the arrival of CDK4/6 inhibitors in the treatment landscape.

EBO: What is HR-positive, HER2-negative breast cancer?

MCANDREW: HR-positive means hormone receptor positive. HER2-negative means the breast cancer does not overexpress the HER2 protein. Hormone receptor positive means positive for either the estrogen receptor or the progesterone receptor. HER2-negative metastatic breast cancer is the most common subtype of breast cancer. Hormone-positive, HER2-negative metastatic breast cancer represents [approximately] 60% to 80% of all cancer diagnoses, with HER2-positive breast cancer being [approximately] 20% and triple-negative breast cancer—meaning it's negative for estrogen, progesterone, and HER2—representing [approximately] 10% of breast cancers.

EBO: What are the goals of therapy in treating patients with this type of breast cancer?

MCANDREW: The main goal of therapy for anybody with metastatic breast cancer—but in particular, hormone-positive, HER2-negative breast cancer—is to control the progression of their cancer. Unfortunately, with metastatic breast cancer, once cancer cells have left the breast and spread to distant organs in the body, or just in lymph nodes in the body not within the regional lymph node chain of the breast tissue, it's no longer curable. Now, of course, the minority of patients develop that. Most patients who have been diagnosed with breast cancer are [diagnosed] at an early stage, but [some] patients either recur or present with de novo metastatic disease. When a breast cancer is not curable, the main goal is to try [to] control the growth of the cancer to try to delay or avoid any kind of complications that could arise from where metastasis can develop. Also, that's in conjunction with helping maintain somebody's quality of life. The main goal of therapy is to prolong someone's life, but also to prolong a good quality of life. That takes into account trying to control the disease, but also especially for hormone-positive, HER2-negative breast cancer, trying to give treatments that will achieve that goal with a minimum amount of toxicity. That's the most important part for hormone-positive, HER2-negative breast cancer.

EBO: Could you give us a brief overview of the current treatment landscape for HR-positive, HER2-negative breast cancer?

MCANDREW: In advanced or metastatic hormone-positive, HER2-negative breast cancer, the broad overview is that, because we're trying to help patients feel as well as possible for as long as possible, you want to start with therapies that are going to be well tolerated and maximally effective. So we prioritize giving hormone-based therapies or hormone-blocking therapies that are usually in conjunction with a molecular therapy. We do that first to try to extinguish those options, because oftentimes, those drugs can be tolerated for a longer period of time and have a better [adverse] effect profile. With chemotherapy, which is traditionally prior to the advent of all these amazing hormone-blocking therapies, we try to use those prior to having to give chemotherapy. In terms of a brief overview, we start off by trying to control the cancer with the less toxic hormone-blocking therapies before moving on to trying to control it with chemotherapy, which is oftentimes more toxic and less effective.

EBO: How has the arrival of the CDK4/6 inhibitors changed the treatment landscape?

MCANDREW: It's been game changing. They've been incredible drugs that have drastically improved survival in patients with metastatic breast cancer—even in the first-line setting. [Traditionally], patients who have first-line metastatic disease for hormone-positive, HER2-negative breast cancer have initially been started on single-agent endocrine therapy; What Dr [Richard] Finn and Dr [Dennis] Slamon [had shown] in their labs is that it was hormone-positive, HER2-negative breast cancer cell lines that seemed to be especially sensitive in a synergistic fashion, with a different therapy to CDK4/6 inhibitors. [This] launched the first of many trials that showed that when we add these compounds to first-line and second-line endocrine therapy, it significantly improves progression-free survival, and importantly, with some CDK4/6 inhibitors, overall survival in both the first- and second-line settings. We have a couple studies now showing that when ribociclib [Kisqali] is added to a first-line endocrine therapy for both premenopausal patients and postmenopausal patients, it significantly improves overall survival.

EBO: What are your preferred treatment regimens for treating patients with HR-positive, HER2-negative advanced breast cancer?

MCANDREW: I take certain things into consideration when I'm trying to select a treatment for patients. The CDK4/6 inhibitors do have different toxicities. For instance, abemaciclib [Verzenio] has more gastrointestinal [GI] toxicity and more diarrhea associated with it, but less neutropenia. It's given on a daily basis rather than a 1 week on 1 week off basis. Ribociclib has less GI toxicity and has [a] more overlapping toxicity profile with palbociclib [Ibrance], with the exception that ribociclib additionally does carry the risk of QT prolongation. For patients whom I'm worried that they're not going to be able to reliably come in [for] electrocardiograms (EKGs) during the first 4 weeks of treatment, I sometimes consider not prescribing that one because I want to make sure they're safe and monitored on therapy. With palbociclib, there's nothing of concern for QT prolongation. However, some of the overall survival data with palbociclib has not been positive. So I generally don't prefer that one when I'm considering between ribociclib and abemaciclib, because the survival data in those drugs has been consistently positive. Those are some of the factors I take into account.

EBO: In addition to concerns about patients coming in for an EKG, has the pandemic affected treatment choices? We know cancer screenings dropped during the early months of the pandemic. Was there any impact on the treatment of metastatic breast cancer?
MCANDREW: In my practice, it hasn’t impacted the treatment of metastatic breast cancer. I certainly think many of the patients who were concerned about coming in for regular follow-ups in regular chemotherapy—especially for patients who were getting treatment for early-stage disease—in the end, I did see some patients concerned about leaving the home during the pandemic, but that’s a minority of patients. I would say most patients were able to come in. [With metastatic breast cancer], these patients are highly motivated to remain in close contact with their oncologist to continue to receive care, so I haven’t seen a major impact when it comes to the availability of treatment and the treatment decisions during the pandemic.

One of the major things, especially early in the pandemic, in the early-stage setting, was that [a lot of] patients who were diagnosed with low-risk hormone-positive or negative early-stage breast cancer—back when the operating rooms were not running at full capacity—were [being] managed with neoadjuvant endocrine therapy until they were able to book their surgery, which was usually months down the line. Typically, these patients will go right to surgery, but because of the institutional decision to try and preserve ventilators for the intensive care unit, and to minimize the number of nonemergent surgeries and elective surgeries, a lot of patients were managed with neoadjuvant endocrine therapy until the operating rooms opened back up at full capacity. That was pretty successful. We didn’t see any delay or anyone’s care be compromised from a cancer perspective. We didn’t see any progressions because of that decision, so that was good.

EBO: Your earlier response about using CDK4/6 inhibitors in first-line treatment is consistent with responses we are hearing from oncologists who treat several types of cancers—that the trend in the first-line setting is to use the best drugs available. Is this true across the board with CDK4/6 inhibitors?

MCANDREW: Yes, absolutely. Often, these drugs are very well tolerated. In many of these studies, patients would have gone on to receive a subsequent CDK4/6 inhibitor. Despite that potential source of confounding in the studies, we still see a maintained overall survival benefit when [we] start by giving them the CDK4/6 inhibitor plus the endocrine therapy. At this point, unless there are patient-specific comorbidities or tolerability [that] preclude the physician from being able to prescribe the CDK4/6 inhibitor, there’s no reason not to start with the CDK4/6 inhibitor. Because when cancers become resistant to a line of therapy, it’s not the same type of cancer, and we don’t know whether delaying the addition of the CDK4/6 inhibitor [is the right thing to do] until they progress on endocrine therapy. Because you’re now dealing with a different type that has already become an acute resistance. So if you capture the opportunity to try to control the disease when it’s as endocrine sensitive as possible with the strongest tools possible, you’re likely offering the patient the maximum amount of benefit.

EBO: Is there anything we haven’t covered that you would like to add?

MCANDREW: The main focus at this point, in terms of where the field is headed, is trying to understand the mechanisms behind CDK4/6 resistance and trying to tailor subsequent therapies to the different ways patients may become resistant to these drugs. I think next-generation sequencing with both liquid biopsies and solid tumor biopsies is going to be a huge part of where we see this field moving in the future. Hopefully we’ll be able to tailor subsequent lines of therapy specifically to patients’ mutations as they arise throughout the course of treatment to stay one step ahead of the cancer. 

REFERENCE


In addition, under special considerations for the use of small-molecule inhibitors, there is updated information on adverse events of special interest, based on evidence published in 2020 by Constantine Tam, MBBS, MD, a hematologist and CLL expert at the Peter MacCallum Cancer Centre in Victoria, Australia.

In December 2021, at the American Society of Hematology Meeting & Exposition in Atlanta, Tam presented results of the SEQUOIA trial, which found that zanubrutinib improved progression-free survival by 58% compared with bendamustine plus rituximab in patients with treatment-naive CLL/SLL; Tam presented results from the cohorts of patients in SEQUOIA who did not have deletion(17p).

REFERENCES


NCCN Updates Give Zanubrutinib Preference in CLL/SLL

Mary Caffrey

CHANGES TO THE National Comprehensive Cancer Network (NCCN) guidelines in chronic lymphocytic leukemia and small lymphocytic leukemia (CLL/SLL) give preference to the Bruton tyrosine kinase (BTK) inhibitor zanubrutinib for several groups of patients, including some receiving first-line therapy. The updates were published on January 18, 2022.1

Zanubrutinib, sold as Brukinsa by BeGenene, is a second-generation BTK inhibitor that has fewer off-target effects and less cardiotoxicity than ibrutinib, a first-generation BTK inhibitor.2

According to the updated guidelines, zanubrutinib is now a preferred therapy for first-line treatment of patients with CLL/SLL who do not have the deletion(17p) / TP53 mutation; the recommendation was given a grade of 2A, which means it is based on lower-level evidence but there is uniform consensus that the recommendation is appropriate.

For patients with CLL/SLL without deletion(17p) / TP53 mutation who are receiving second-line or subsequent therapy, zanubrutinib was moved from “other recommended regimen” to “preferred regimen.” The statement that recommended zanubrutinib to patients with a contraindication to other BTK inhibitors was removed.

For both updates, the recommendations extended to patients older or younger than 65 years, with or without comorbidities. For those patients who have CLL/SLL with the deletion(17p) / TP53 mutation zanubrutinib is now a preferred therapy in both first- and second-line treatment, according to the updated guidelines. Again, zanubrutinib was moved from “other recommended regimen” to “preferred regimen,” and the qualifying statement that the drug be given to patients with a contraindication to other BTK inhibitors was removed.

In addition, under special considerations for the use of small-molecule inhibitors, there is updated information on adverse events of special interest, based on evidence published in 2020 by Constantine Tam, MBBS, MD, a hematologist and CLL expert at the Peter MacCallum Cancer Centre in Victoria, Australia.

In December 2021, at the American Society of Hematology Meeting & Exposition in Atlanta, Tam presented results of the SEQUOIA trial, which found that zanubrutinib improved progression-free survival by 58% compared with bendamustine plus rituximab in patients with treatment-naive CLL/SLL; Tam presented results from the cohorts of patients in SEQUOIA who did not have deletion(17p).
24-hour inhibition of BTK was maintained at 100% in PBMCs and 94% to 100% in lymph nodes when taken at the recommended total daily dose of 320 mg. The clinical significance of 100% inhibition has not been established.1,2

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage
Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage events including intracranial and gastrointestinal hemorrhage, hematuria and hemotherax have been reported in 3.4% of patients treated with BRUKINSA monotherapy. Hemorrhage events of any grade occurred in 35% of patients treated with BRUKINSA monotherapy. Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage. Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections
Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 27% of patients, most commonly pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred. Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

Cytopenias
Grade 3 or 4 cytopenias, including neutropenia (26%), thrombocytopenia (11%) and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy. Grade 4 neutropenia occurred in 13% of patients, and Grade 4 thrombocytopenia occurred in 3.6% of patients. Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose or discontinue treatment as warranted. Treat using growth factor or transfusions, as needed.

Second Primary Malignancies
Second primary malignancies, including non-skin carcinoma, have occurred in 14% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 8% of patients. Other second primary malignancies included malignant solid tumors (4.0%), melanoma (1.7%) and hematologic malignancies (1.2%). Advise patients to use sun protection, and monitor patients for the development of second primary malignancies.

Cardiac Arrhythmias
Atrial fibrillation and atrial flutter were reported in 3.2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension and acute infections may be at increased risk. Grade 3 or higher events were reported in 1.1% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Embryo-Fetal Toxicity
Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for 1 week after the last dose. Advise men to avoid fathering a child during treatment and for 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

ADVERSE REACTIONS

The most common adverse reactions, including laboratory abnormalities, in ≥ 30% of patients who received BRUKINSA (N=847) included decreased neutrophil count (54%), upper respiratory tract infection (47%), decreased platelet count (41%), hemorrhage (35%), decreased lymphocyte count (31%), rash (31%) and musculoskeletal pain (30%).

DRUG INTERACTIONS

CYP3A Inhibitors: When BRUKINSA is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA dose to 80 mg once daily. For co-administration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

CYP3A Inducers: Avoid co-administration with moderate or strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment: The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.

Please see Brief Summary of full Prescribing Information on following pages.
THE BTK INHIBITOR THAT DELIVERS POWERFUL AND CONSISTENT RESPONSES

BRUKINSA\(^1\) (zanubrutinib) is a kinase inhibitor indicated for the treatment of adult patients with Waldenström’s macroglobulinemia.

A global, randomized Phase 3 trial in WM across a range of patients\(^1\)
- Treatment-naive
- Relapsed/refractory

\(^1\)CR+VGPR+PR

\(^2\)VGPR/CR

\(^3\)PR

Powerful Responses Across WM Patients

While the primary endpoint of superiority did not reach statistical significance, numerically higher VGPR/CR rates were achieved in the BRUKINSA treatment arm.\(^1\)

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Median follow-up time was 19.4 months.\(^7\)
The prespecified efficacy outcome measure of VGPR/CR was assessed by IRC.\(^1\)

Safety in WM is consistent with the established BRUKINSA profile\(^1\)

Serious adverse reactions, including fatal events, have occurred with BRUKINSA, including hemorrhage, infections, cytopenias, second primary malignancies, and cardiac arrhythmias. The most common adverse reactions (≥30%) include neutrophil count decreased, upper respiratory tract infection, platelet count decreased, hemorrhage, lymphocyte count decreased, rash, and musculoskeletal pain.

References:
Indications and Usage

1.1 Mantle Cell Lymphoma

BRUKINSA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate (see Clinical Studies 14.1). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.2 Waldenström's Macroglobulinemia

BRUKINSA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

1.3 Marginal Zone Lymphoma

BRUKINSA is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen.

This indication is approved under accelerated approval based on overall response rate (see Clinical Studies 14.2). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

4.2 Interactions

Avoid co-administration of BRUKINSA with moderate or strong CYP3A inducers (e.g., phenobarbital, phenytoin, rifampin, St. John's Wort) because BRUKINSA is a substrate of CYP3A. Avoid concomitant use or co-administration with strong CYP3A inhibitors because CYP3A inhibition may lead to decreased BRUKINSA exposure (see Data 3.3).

5.2 Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematologic malignancies treated with BRUKINSA monotherapy, Grade 3 or higher infections including intracranial and gastrointestinal hemorrhage, hematoma and hemorrhage have been reported in 34% of patients treated with BRUKINSA monotherapy. Hematoma events of any grade, excluding purpura and petechiae, occurred in 30% of patients. Bleeding events have occurred in patients with and without concomitant anticoagulation or antithrombotic therapy.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

5.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (46%), thrombocytopenia (11%) and anemia (8%) based on laboratory measurements, developed in patients treated with BRUKINSA monotherapy (see Adverse Reactions 6.1). Grade 4 neutropenia occurred in 13% of patients, and Grade 4 thrombocytopenia occurred in 36% of patients. Complete blood counts regularly during treatment and interrupt treatment, reduce the dose, or discontinue treatment as warranted (see Dosage and Administration 2.4). Treat using growth factor transfusions or, as needed.

5.4 Secondary Malignancies

Secondary malignancies, including non-skin carcinoma, have occurred in 14% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 8% of patients. Other secondary malignancies included myelodysplastic syndrome (4%), melanoma (1.7%) and hematologic malignancies (1.2%). Advise patients to use sun protection and monitor patients for the development of secondary malignancies.

5.5 Cardiac Arrhythmias

Atrial fibrillation and atrial flutter were reported in 3.2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.8% of patients. Advise patients to stop BRUKINSA treatment as warranted and manage as appropriate (see Dosage and Administration 2.4).

6.1 Clinical Trials Experience

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

The data in the WARNINGS AND PRECAUTIONS reflect exposure to BRUKINSA in severe clinical trials, administered as a single agent at 160 mg twice daily in 730 patients, at 320 mg once daily in 105 patients, and at 40 mg to 160 mg once daily in 160 patients (N=118).

In this pooled safety population, the most common adverse reactions, including laboratory abnormalities, in ≥ 30% of patients included neutropenia count decreased (54%), upper respiratory tract infection (47%), platelet count decreased (45%), hemoglobin decreased (36%), lymphopenia count decreased (31%), rash (31%), and musculoskeletal pain (30%). Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hematopoietic 0%).

Table 3: Adverse Reactions (≥ 10%) in Patients Receiving BRUKINSA in BGB-3111-206 and BGB-3111-AU-003 Trials

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>Percent of Patients (N=118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
<td></td>
</tr>
<tr>
<td>Hematologic abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia decreased</td>
<td>45</td>
<td>20</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>40</td>
<td>7</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>41</td>
<td>16</td>
</tr>
<tr>
<td>Chemistry abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric acid increased</td>
<td>29</td>
<td>2.6</td>
</tr>
<tr>
<td>ALT increased</td>
<td>28</td>
<td>0.9</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>24</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Table 8 summarizes selected laboratory abnormalities.

Laboratory Parameter | Percent of Patients (N=118) |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Hematologic abnormalities</td>
<td></td>
</tr>
<tr>
<td>Neutropenia decreased</td>
<td>45</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>40</td>
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<td>28</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>24</td>
</tr>
</tbody>
</table>

* Includes fatal adverse reaction.

** Based on laboratory measurements.

† Hypoglycemia: hypoglycemia is a known effect of ET. resolution.

<table>
<thead>
<tr>
<th>Waldenström's Macroglobulinemia (WM)</th>
</tr>
</thead>
</table>
| The safety of BRUKINSA was investigated in two cohorts of Study BGB-3111-302 (ASPEN). Cohort 1 included 199 patients with MYD88 mutation (MYD88*) WM, randomized to and treated with either BRUKINSA (101 patients) or ibrutinib (98 patients). The trial also included a non-randomized arm, Cohort 2, with 26 wild type MYD88 (MYD88**) WM patients and 2 patients with unknown MYD88 status (see Clinical Studies 14.2).

Among patients who received BRUKINSA, 93% were exposed for 6 months or longer, and 68% were exposed for greater than one year.

In Cohort 1 of the ASPEN safety population (N=101), the median age of patients who received BRUKINSA was 70 years (45-87 years old); 67% were male, 33% were female. 4% were Asian and 10% were not reported (unknown race). In Cohort 2 of the ASPEN safety population (N=26), the median age of patients who received BRUKINSA was 72 (39-87 years old); 50% were male, 50% were female and 4% were not reported (unknown race).

In Cohort 1, serious adverse reactions occurred in 44% of patients who received BRUKINSA. Serious adverse reactions in < 2% of patients included hemorrhage (4%), hemoptysis (4%), febrile neutropenia (3%), sepsis (2%), cellulitis (2%), and 2 patients experienced a fatal event of COVID-19 pneumonia.

Table 3: Adverse Reactions (≥ 10%) in Patients Receiving BRUKINSA in BGB-3111-206 and BGB-3111-AU-003 Trials
of 0 to 1. Patients had a median of 2 prior lines of therapy (range: 1 to 4). The BGB-3111-206 trial required a platelet count

Mantle Cell Lymphoma (MCL)

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration

5.4 Second Primary Malignancies

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs.

Musculoskeletal and connective tissue disorders

Vascular disorders

Hemorrhagei 23 1.1

Hematologic Abnormalities

Laboratory Abnormalities1) (≥ 20%) That Worsened from Baseline in Patients with WM Who Received BRUKINSA in Cohort 1

Table 6: Select Laboratory Abnormalities1) (≥ 20%) That Worsened from Baseline in Patients with WM Who Received BRUKINSA in Cohort 1

Upper respiratory tract infection includes upper respiratory tract infection, bronchitis, pneumonia, noninfectious aspiration, aspiration event.

1) Includes all reported treatment-emergent “events,” “adverse events,” or “adverse reactions.”

Hematologic Abnormalities

Neutrophils decreased in patients with hepatic impairment estimated by Cockcroft-Gault. Monitor for BRUKINSA adverse reactions in patients on dialysis which may increase the risk of BRUKINSA toxicities.

Chemistry abnormalities

Table 7: Adverse Reactions Occurring in ≥ 10% Patients with MCL Who Received BRUKINSA

Healthy volunteers were evaluated in all patients previously treated in two single-arm clinical studies, BIBS-3111-A012 and BIBS-3111-A013 (see Clinical Studies (14.3)). The trials required an absolute neutrophil count ≥ 1 x 10^9/L, platelet count ≥ 50 x 10^9/L, and adequate hepatic function and excluded patients requiring a strong CYP3A inhibitor or inducer. Patients received BRUKINSA 160 mg twice daily (673) or 320 mg once daily (356). The median age in both studies combined was 67 years (range 17 to 83). 256 patients (59%), 164 patients (53%), and 11% had an Eastern Cooperative Oncology Group performance status of 0 to 1, 2, or 3, respectively. Presently, BRUKINSA was evaluated in 118 patients with MCL in a single-arm, phase 2 clinical study, BIBS-3111-A010. In this study, patients received BRUKINSA 160 mg daily at the recommended dose level of 160 mg twice daily, or 320 mg once daily. The majority of patients (78%) had an Eastern Cooperative Oncology Group performance status of 0 to 1.

Some data may be indirect or include mortality data.

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7.1 Effect of Other Drugs on BRUKINSA

Table 9: Drug Interactions That Affect Zanubrutinib

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Serious adverse reactions occurring 40% of patients. The most frequent serious adverse reactions were pneumonitis (8%) and pneumonitis (7%).

Adverse reactions leading to treatment discontinuation in 6% of patients, dose reduction in 2.3%, and dose interruption in 34%. The leading cause of dose modification was respiratory tract infection (15%).

Table 7: Adverse Reactions Occurring in ≥ 10% Patients with MCL Who Received BRUKINSA

Table 8: Select Laboratory Abnormalities1) (≥ 20%) That Were Worse from Baseline in Patients with WM Who Received BRUKINSA

Infections and infestations

Upper respiratory tract infection1) 26 3.4

Infections and infestations

Vasculitis disorders

Skin conditions and subcutaneous tissue disorders

Nervous system disorders

Respiratory, thoracic and mediastinal disorders

Hemoglobin decreased 26 6

Table 8: Adverse Reactions in Cohort 1 in A1SPEN

Table 5: Adverse Reactions in Cohort 1 occurring in ≥ 10% Patients in WM Who Received BRUKINSA

Moderate and Strong CYP3A Inhibitors

Prevent or management

Lymphocytes decreased 32 8

Table 10: Laboratory Abnormalities1) (≥ 20%) That Were Worse from Baseline in Patients with MZL

Laboratory abnormality1) of 0 to 1. Patients had a median of 2 prior lines of therapy (range: 1 to 4). The BGB-3111-206 trial required a platelet count

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration

Chemistry abnormalities

Glucose decreased 54 4.6

Table 9: Drug Interactions That Affect Zanubrutinib

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration

Moderate and Strong CYP3A Inducers

Prevent or management

Hemoglobin decreased 26 6

Chemistry abnormalities

Glucose increased 54 4.6

Hemoglobin decreased 26 6

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration
TENNESSEE ONCOLOGY, BASED IN Nashville, has announced new leadership roles for medical oncologist Stephen Schleicher, MD, MBA, and Natalie Dickson, MD, a medical oncologist/hematologist who most recently served as president and chief medical officer (CMO).

Effective January 1, Schleicher became CMO: Dickson remains president while taking on the new role of chief strategy officer (CSO).

Ron Horowitz remains the CEO, and Jeff Patton, MD, formerly CEO, is board chair. Additionally, Patton is now CEO of OneOncology, a network of community-based oncology practices that wish to maintain independence while partnering to leverage data and technology, clinical pathways, pharmacy and therapeutics, and clinical trial participation.

According to a statement from Tennessee Oncology, Dickson will focus on Tennessee Oncology’s growth and long-term strategy while Schleicher will oversee clinical programs “to promote the high-quality, innovative, and patient-centered care Tennessee Oncology is known for delivering.” The community practice has more than 190 providers across 33 clinics in Tennessee and northern Georgia.

Dickson is credited with facilitating Tennessee Oncology’s entrance into the Oncology Care Model (OCM), creating an internal palliative care program, developing a financial counseling team, and creating integrated oncology and genetics counseling programs. Schleicher, who has served as medical director for value-based care for Tennessee Oncology and OneOncology, received perfect scores in the OCM while saving millions of dollars, secured certification from the American Society of Clinical Oncology (ASCO), and formed one of the largest commercial oncology medical home programs with Ascension and Blue Cross Blue Shield of Tennessee.

Schleicher, who is a member of the Evidence-Based Oncology™ (EBO) editorial board, and Dickson discussed their new roles and upcoming challenges in community oncology. This interview has been edited lightly for clarity.

EBO: Dr Schleicher, can you discuss your new role and responsibilities as CMO at Tennessee Oncology?

SCHLEICHER: In my new role as chief medical officer at Tennessee Oncology, I will continue working very closely with Dr Dixon, who has been our previous chief medical officer and president, and she will remain president [along] with [taking on] her new role, chief strategy officer. Tennessee Oncology has done a great job over the last 5-plus years of making itself [into] a unique, world-class cancer organization in the community. [Much] of that relies on internal maximization of quality, on innovation, and on a drive toward value. My goal is to continue to support that internally and help that grow, so we can continue to be a unique, high-quality, comprehensive service offering in the community. [This] includes a push of innovation toward value; we’ll continue that. It [includes] helping us clinically; to continue top-notch, evidence-based care at all of our 30-plus clinic sites; to continue to support expansion of services, such as psychology, genetics, integrative oncology, and other things that every patient, wherever they may live, needs access to; and to really make sure that all of our clinics can continue to provide that high-quality, comprehensive care. And, we will continue to push innovation, just as Dr Dixon has done in her many years as CMO before this.

EBO: Dr Dickson, similar question: Can you please explain your new role and responsibilities as CSO and how they expand your responsibilities as president?

DICKSON: As president, my goal is to enhance a culture that promotes the highest quality of care across our clinical and our ancillary sites, and in this way accomplish our mission. I’m also involved in looking at ways to improve service excellence and patient-centered care, and ensuring that we have the resources for continuous improvement and for innovation. It’s also my role—and it’s really important—to help create a highly attractive practice environment, not just for physicians, but also the staff, and to foster their professional development and their personal well-being. So, in my expanding role as chief strategy officer, I will work closely with our CEO and our executive team to provide strategic and visionary input to advance the transformation of care delivery, and to seek new opportunities for growth. It will be important for me to strengthen our partnerships, to make new relationships, and to identify new processes, technology, and new business opportunities. As Dr Schleicher alluded to just now, so many exciting things are happening at Tennessee Oncology: We have specialized teams working on patient monitoring and patient communication; [we are] expanding our data analytics capabilities, [with] the addition of new technologies to support care coordination; new medical home programs, in partnership with payers; and partnerships with local hospital systems to enhance comprehensive care. [We are] developing clinical trial research through [our] comprehensive precision medicine program, and the steady addition of new clinics. And so, it’s important that my actions and decisions as CSO help bolster these initiatives.

EBO: What are some of the biggest challenges ahead for Tennessee Oncology, specifically, and for community oncology more broadly over the next several years?

DICKSON: Government policy changes, as a burden of utilization management, remain our biggest risk and challenge. Government policy changes can have sweeping effects on our reimbursement, such as the recently abandoned “most favored nation” policy and the recent update on the in-office ancillary service exemption. Utilization management—including things like step edits, prior authorization, and formulary control—remain really burdensome for practices, especially practices like ours [that] are already investing in and adhering to evidence-based clinical pathways. So, it’s really important for community oncology to continue to advocate through [the Community Oncology Alliance] and our specialty societies. But we face many more challenges. Pharmacy benefit managers are redirecting patients away from in-practice pharmacists, which prevents our patients from benefiting from our practices’ compliance and toxicity monitoring. Obtaining access to real-time patient data is challenging, but it’s really necessary to be able to participate successfully in value-based care programs. And it is critical if a practice is taking on downside risk.

And then, don’t forget the cost of a data warehouse—this is often prohibitive for small practices. Practices are being bombarded by a multitude of technology and service vendors, and it’s hard to evaluate and determine their value. Many practices don’t have the expertise to take this on. Tennessee Oncology is able to leverage the expertise of OneOncology to help in this regard. Of course, there are new players on the market; some offer some level of competition, and others just increase...
the complexity of the management of our cancer patients—things like infusion centers, or pathology groups that are vying for access to a patient's tissue. But despite all this, if we remain patient focused, and true to our mission, and engaged in health policy reform, I'm confident that community oncology will weather the storm and the many challenges to vaccine.

**EBO:** Dr Dickson, OneOncology has been at the forefront of the discussion of the need for 340B reforms to create a fair playing field for community oncology. How have these trends affected Tennessee Oncology? And how have you responded as practice?

**“Our hope is that Medicare has a follow-up model to the OCM [Oncology Care Model] at some point, because just as we learned so much through OCM; we want to continue to learn through future models. We hope that there’s a bridge between models, but not an end to the model for Medicare, because that is such a large patient population. And those enhanced services payments allowed us to build these programs.”**

---Stephen Schleicher, MD, MBA, chief medical officer, Tennessee Oncology; medical director for value-based care, OneOncology

**DICKSON:** The 340B program was developed to help patients in need, and especially those patients with cancer. Unfortunately, it has been determined that, by and large, hospitals have not increased their uncompensated care once they’ve entered this 340B program. Tennessee Oncology continues to be the primary provider of free cancer care in our market. And we treat and manage all patients who grace our clinics, regardless of whether they’re insured. We think it’s just the right thing to do. You know, in 2021, we were able to provide more than $70 million in free drug. We see that patients continue to pay very high prices at hospitals, and the prices are much higher than in the community setting. What we can do is continue to advocate for fairer pricing and for price transparency. And we will also try to make data available to health policy researchers. We will continue to demonstrate our value, to demonstrate our value proposition to our patients and our communities and health plans and the employers.

Our value proposition is that we provide the highest quality of care with the lowest cost for drugs, for radiation, and for imaging for labs; and we also continue to provide cutting-edge clinical research and comprehensive supportive care services for our patients close to their homes. You know, I think it’s in the best interest of patients, health plans, and employers to shift all expensive treatments from the hospital to the community. And if we share our data, and share our experiences, I think we may accelerate this transition.

**EBO:** Let’s transition to the OCM. Dr Schleicher, over the past few years, Tennessee Oncology has seen great success in the OCM, saving Medicare millions of dollars and achieving perfect quality scores. Can you please describe what Tennessee Oncology plans to do after the end of the OCM this summer?

**SCHLEICHER:** Great question. We’ve learned so much by participating in the OCM—[to start], how to reduce hospitalizations and emergency [department] visits, and how to incorporate pathways into care, to make sure patients get the right care at the right time. We’ve centralized our triage teams; we centralized responding to patient illness and issues in the acute setting. We’ve centralized care coordinators to proactively reach out to patients. So, we’ve done all these things, and it’s helped us learn how to improve quality of care. We know that’s the right thing to do—as Dr Dixon mentioned, our mission is to have the highest quality care possible in the community [while] lowering cost by keeping people out of the hospital, etc. We’ve incorporated palliative care, etc. So, with all these things that we’ve learned from OCM, we have no inclination to stop doing that just because the model ends. We’ll continue to provide these resources to patients. It’s great that we’ve learned this, and we’re large enough that we can continue.

We’ve tried to use what we’ve learned and to apply this to the non-Medicare population as well. We’re in one of the largest commercial Oncology Medical Homes in the country through our partnership with Blue Cross Blue Shield, and that’s also partially through Ascension, which we have a partnership with. And we’re in several other medical homes; we’re one of 11 practices to be working toward ASCO Medical Home accreditation. We have no goal to put on the brakes here; instead, we want to continue to drive value, which also drives innovation in patient care. Our hope is that Medicare has a follow-up model to the OCM at some point, because just as we learned so much through OCM; we want to continue to learn through future models. We hope that there’s a bridge between models, but not an end to the model for Medicare, because that is such a large patient population. And those enhanced services payments allowed us to build these programs. So, we have every intention to continue doing what we’ve been doing—even broadening [it] to commercial populations. But we do hope that Medicare has an upcoming value-based care model as well, because we’d hate to have learned all these things, and not have a model to apply it to, even though we’ll continue to apply it to our patients.

**EBO:** Where do you see advances in value-based care going from here? How much leadership will come from Medicare, and how much innovation is happening in the commercial sector?

**SCHLEICHER:** Medicare obviously was extremely influential in teaching us about value-based care in oncology through the OCM. Oncology is very different from other types of specialty care, especially primary care, because within cancer are [more than] 100 different diseases. Every patient is different—how do you account for that? Drugs, unfortunately, whether we like it or not, are the elephant in the room—drugs make up a huge part of the cost. So how does that go into a model?

We’re really, really incentivized to keep people out of the hospital. Yet, [for example], Keytruda [pembrolizumab], one of the best drugs we have, is still very expensive. How do we balance all that? So, Medicare has taught us a lot.

Now, as OCM is ending—and hopefully [it represents] just a bridge toward something else for Medicare—I really applaud our commercial payers. At least in Tennessee, I can [cites] [several] that have come to us either with attempts to co-create models, or bring value-based care models to us, largely stemming from the OCM. But our hope is to make each model that much more innovative, so that we can continue to drive value, even in the absence of a Medicare model right now.

Some real pluses—with commercial payers, it’s obviously very different. For large practice, if you’re talking to a large commercial payer, like Blue Cross, we just co-created a medical home with them. [After] being one of 180 practices talking to Medicare about OCM, now we really get a chance to co-design models, which is excellent, because it allows us to take what we’ve learned from being participants in a 5- or 6-year government pilot and apply that to a more nuanced model that fits our patient population—and really align where costs are and what we can actually control. A big plus with commercial [payers] is the ability to co-create.

Two, there’s data sharing, which is a problem with OCM. As I understand it, [with the OCM] after 18 months, you get the full reconciliation report and know how you did. With commercial models, where it’s just 1 big practice and 1 large commercial payer, we’re able to share data much more quickly and get feedback to drive innovation much faster than an 18-month PDMA [plan, do, study, act] cycle. So, that’s another big plus.

And then third, it expands the population who gets access to these great services that we’ve begun to offer through OCM. Now, we’re able to apply it across broader patient populations; more patients benefit. Something else that comes up a lot is health care disparities, and we’ve found that a lot of what we’ve learned and created in response to OCM disproportionately impact patients who live in rural areas. By engaging through [patient-re- ported outcomes], our care navigators, and our coordinators, [we’ve reached] a large population of these patients who live 30 miles outside of metropolitan areas; to be being able to take those great benefits and apply [them] to the large commercial population is another big win. … As we wait for the next model, a lot of innovations are happening with commercial payers, and it’s a great extension from what we learned from OCM. Hopefully, we continue to innovate even faster, and bring that back to the Medicare population when the next model comes.
Emory’s Winship Joins AccessHope as Collaboration Partner

ACCESSHOPE HAS ADDED a fourth partner to its group of National Cancer Institute (NCI)-designated cancer centers that will collaborate in offering remote delivery of expertise to members of employer health plans.

Winship Cancer Institute of Emory University in Atlanta, Georgia, will serve members of AccessHope employer health plans in southeastern states, including Alabama, Florida, Georgia, Mississippi, North Carolina, South Carolina, and Tennessee.

Winship joins City of Hope in Duarte, California; the Robert Lurie Comprehensive Cancer Center of Northwestern University in Chicago, Illinois; and Dana-Farber Cancer Institute in Boston, Massachusetts, in offering the core services of AccessHope: accountable precision oncology, expert advisory review, and cancer support teams. AccessHope is a program that allows patients and community oncologists to tap into the expertise of City of Hope, often through electronic sharing of records so the patient does not have to travel. “[Patients] deserve access to the latest cancer care knowledge, regardless of their geographic location. The ability to remotely access health information has become increasingly important for the patient experience, particularly during the COVID-19 pandemic when [the] ability or willingness to travel for cancer care may have been impacted,” Mark Stadler, CEO of AccessHope, said in a joint statement from AccessHope and Emory Healthcare.

“As we continue connecting plan members and their local treating oncologists with these world-renowned specialists who can review their cases, our primary goal is to share insights they can use to optimize cancer treatment plans and improve clinical outcomes,” Stadler said.

Emory Healthcare, with 24,000 employees, 11 hospital campuses, and more than 3300 physicians across more than 70 specialties, operates across Georgia in 250 locations.

“Patients are at the center of everything we do, and our mission is to improve lives and provide hope,” Jonathan S. Lewin, MD, executive vice president for health affairs of Emory University and CEO of Emory Healthcare, said in the statement. “Through innovation and discovery, our clinicians and cancer specialists are focused on advancing medical research and progressive cancer treatments that will benefit those who receive a cancer diagnosis, and we are pleased to collaborate with AccessHope to provide further access to patients in need of cancer expertise.”

Winship is Georgia’s only NCI-designated Comprehensive Cancer Center; it is ranked in the top 50 in the United States and first in Georgia for cancer care, according to US News & World Report. Winship clinicians see more than 17,000 patients with new diagnoses each year. Construction is underway on a 17-story cancer facility, representing the largest expansion in Winship’s history.

In the research realm, investigators enrolled more than 900 participants in more than 300 clinical trials in 2020, the same year Winship received $80 million in research funding. As is the case elsewhere, Winship is seeing more patients with later-stage cancers. “Winship oncologists are seeing a recent trend of more patients coming through our doors with advanced or later-stage cancers, which likely progressed from delayed screenings or treatment during the COVID-19 pandemic,” said Sagar Lonial, MD, FACP, chief medical officer of Winship Cancer Institute of Emory University. “Through our new collaboration with AccessHope, Winship clinicians will provide valuable medical expertise for patients with complex cancers, including our multidisciplinary teams that care for head and neck, lung, prostate and breast cancers, as well as the rapidly changing field of blood cancers. Those experts can then provide recommendations to local oncologists so individuals receive state-of-the-art care as quickly as possible.”

A survey by the American Hospital Association ranked Emory Healthcare as one of the top 10 most-trusted health care brands in the United States and the top health care system in Georgia. Consumers who were surveyed reported that 3 strategies were paramount to boost trust: being transparent and clear with information, listening and being empathetic, and offering care and treatment choices to patients.

“Improving access, increasing options, and expanding health literacy can go a long way in addressing critical issues in health care such as health disparities, trust in health care and health care providers, and patients proactively seeking out specialized medical care. AccessHope’s unique approach in connecting people with cancer expertise, regardless of their geographic location, was a natural fit for Emory Healthcare and Winship Cancer Institute, where patients come first,” says Dane Peterson, president and chief operating officer of Emory Healthcare, said in the statement.

Results of a recent study published in JCO Oncology Practice found that AccessHope clinicians’ expertise influences the course of care in lung cancer cases. NCI-level subspecialists who provided evidence-based recommendations through the program influenced 93% of the cases AccessHope received, the results showed. Accompanying the clinical and humanistic benefits was an average of $19,000 in cost savings per plan member.

AccessHope serves approximately 3.3 million plan members who have access to its cancer support services through 75 employers and collaborative relationships with Collective Health via its Premier Partner Program and with Health Transformation Alliance and Quantum Health.

REFERENCES


Developers Are Advised to Challenge Regulatory Standards to Speed Development of Biosimilars

MEIR RINDE, MS

DEVELOPERS CAN BRING BIOSIMILARS to market more quickly and at lower cost by challenging regulatory requirements and restricting testing of these agents to analytical similarity and clinical pharmacology, Sarfaraz K. Niazi, PhD, wrote in a December 2021 paper in the journal *Expert Opinion on Biological Therapy*. Niazi is an adjunct professor of biopharmaceutical sciences at the University of Illinois and the University of Houston, founder of the biosimilars companies Karyo Biologics and Adello Biologics, and an Advisory Board member of The Center for Biosimilars®.

After analyzing regulatory documents for more than 100 biosimilars, Niazi concluded that excluding the other main processes contributing to approvals—animal testing and clinical efficacy testing—would not have changed any approval decisions. Niazi, who has previously challenged FDA and World Health Organization biosimilar approval guidelines, said the agencies will not reject rational scientific plans that dispense with tests that do not provide helpful information. They have modified and relaxed many requirements in recent years, he said.

“While the agencies may be slower in changing their guidelines, the onus lies on the developers to challenge the guidelines to restrict the testing to analytical similarity and clinical pharmacology. Even these testings can be reduced significantly without compromising their value to establish biosimilarity.” Niazi wrote.

Future challenges will lead to “a new era of faster, lower-cost approval of biosimilars without risking their safety and efficacy,” explained Niazi.

Animal testing is not helpful for biosimilar approvals because differing animal and human pharmacodynamics mean toxicology studies do not provide useful data, Niazi said. No biosimilars have failed in animal toxicity testing, “because they cannot.”

In the past, the FDA has often declined to evaluate animal studies of biosimilars, and its Center for Drug Evaluation and Research is now encouraging use of new-approach methodologies, Niazi wrote. Alternative approaches include human and animal cells, organoids, organ-on-chips, and in silico modeling.

Organoids are multicellular constructs that mimic the activity or tissue environment of human organs. Organ-on-chips are devices that mimic the human physiological and mechanical environment for the purposes of medical study, and in silico models are digitized representations of pharmacologic and physiologic processes.

Niazi provided several arguments for why developers should avoid clinical efficacy studies. Comparing supposedly identical products is “a statistical challenge” based on “arbitrary assumptions,” he wrote. The FDA allows use of pharmacokinetic and pharmacodynamic (PD) biomarker data in healthy patients instead, which generally requires shorter, less costly studies and produces more sensitive results. The agency has already licensed several products on PD evaluation only.

Efficacy testing is mostly “a checkmark item” that “constitutes unnecessary human exposure,” Niazi wrote.

Further, Niazi said that clinical studies of comparative equivalence are not useful, as they are unlikely to fail and have never resulted in the rejection of biosimilarity. They are also difficult to conduct for some drugs, such as anticancer agents, for which recruitment of homogeneous populations or comparable patients is a challenge.

In the future, regulators will approve biosimilars based solely on analytical assessment and clinical pharmacology profiling. Niazi argued. These areas can also be made less complex. He advises developers to avoid orthogonal testing during analytical assessment and follow agency recommendations that they explore creative methods, such as using ultraviolet and fluorescence spectroscopy to compare secondary and tertiary structures.

Novel testing modalities should also be considered for clinical pharmacology comparisons. Niazi suggested using narrow criteria for study subjects in order to reduce study sizes. He also recommended consolidating all expected outcomes in a single study, while at the same time avoiding unnecessary meetings with FDA officials to prevent development plan delays.

REFERENCE


Bevacizumab Biosimilar Candidate Demonstrates High Similarity to Avastin in NSCLC

THE PROPOSED BIOSIMILAR MYL-14020 (Aberyum; Viatris and Biocon Biologics) met predefined criteria for biosimilarity to reference bevacizumab in a phase 3 trial in patients with stage IV nonsquamous non–small cell lung cancer (nsNSCLC).

The authors noted that lung cancer is the most common cause of cancer-related mortality in the United States and worldwide. Bevacizumab, a monoclonal antibody to VEGF-A, retards blood vessel development that supports tumor growth. The reference product (Avastin) was approved to treat metastatic colorectal cancer by the FDA in 2004 and by the European Medicines Agency (EMA) in 2005. Today, bevacizumab is authorized for multiple indications, including in combination with platinum-based chemotherapy as a first-line treatment for patients with advanced or recurrent nsNSCLC.

In many cancers, bevacizumab-based regimens have improved overall survival (OS) and progression-free survival (PFS); however, patient access can be limited due to high-out-of-pocket costs.
the authors said. Bevacizumab “has become an integral, standard-of-care component for many malignancies,” and biosimilars, which are often lower-cost alternatives to reference products, could improve access.

Previous studies have established the analytical and pharmacokinetic similarity of MYL-1402O to reference bevacizumab. The current study evaluated efficacy, safety, and immunogenicity of MYL-1402O compared with the reference product in combination with carboplatin and paclitaxel (CP) chemotherapy in patients with stage IV non–small-cell lung cancer (NSCLC). The study included 671 patients from 102 sites in 17 countries. After randomization, patients were treated with reference bevacizumab or the biosimilar plus CP for up to 18 weeks (6 cycles), followed by monotherapy with the reference drug or the biosimilar for up to 24 weeks.

Similar Overall and Progression-Free Survival Rates
The primary end point was overall response rate (ORR) at 18 weeks. The authors, noting that “the FDA and the EMA use different approaches to determine equivalence based on the ORR,” reported ORR consistent with both FDA (ratio of ORR) and EMA (difference in ORR) requirements. Overall, 41.5% and 43.1% of patients in the biosimilar and originator groups, respectively, had either a complete or partial response at 18 weeks. Efficacy based on ORR was comparable between groups. The ratio of ORR between groups was 0.96 (90% CI, 0.83-1.12) and the difference in ORR between groups was −1.6 (90% CI, −9.0 to 5.9). The 90% confidence intervals were within predefined margins for biosimilarity. The authors noted that “the ORR data reported here are within the range of ORR reported in published data for the reference product.”

Subgroup analyses were carried out based on age, sex, race, smoking status, number of metastasis sites, prior radiation therapy, ECOG status, negative or unknown sensitizing EGFR mutation, negative or unknown sensitizing EML4-ALK rearrangement, and geographical region. Overall, the authors said, these results supported equivalence between the treatment groups; however, when the number of metastasis sites was limited to 1 and patients had had prior radiation therapy, there was evidence of a “slightly lower response” in the biosimilar group.

In many cancers, bevacizumab-based regimens have improved overall survival and progression-free survival; however, patient access can be limited due to high out-of-pocket costs.

The investigators reported that secondary efficacy end points—including PFS, OS, disease control rate, and duration of response at 18 weeks and 42 weeks—were comparable between groups. For example, the median PFS at 42 weeks was 7.6 months (95% CI, 7.0-9.5) in patients treated with MYL-1402O and 9.0 months (95% CI, 7.2-9.7) in patients treated with reference bevacizumab.

Adverse Events “Within the Expected Range”
On safety, the authors wrote, “the frequency, type, and severity of treatment-emergent adverse events (TEAEs) and AEs of interest were comparable between MYL-1402O and reference bevacizumab, falling within the expected range of the type and severity previously described in other bevacizumab biosimilar studies.”

Most patients (92.8% in the biosimilar group and 92.4% in the originator group) reported at least 1 TEAE during the study. The authors noted there were 8 (2.4% of patients) and 5 (1.5% of patients) TEAEs leading to death in the biosimilar and reference product groups, respectively, considered to be related to bevacizumab treatment. They also noted there was a higher incidence of serious TEAEs during the bevacizumab-plus-CP treatment period compared with the bevacizumab monotherapy period.

The investigators observed “no notable differences” between groups in treatment-emergent antidrug antibodies (ADAs), with 6.5% of patients treated with MYL-1402O and 4.8% of patients treated with the originator positive for ADAs. The incidence of neutralizing antibodies was lower in the biosimilar group (0.6%) compared with the originator group (2.5%).

The authors concluded that MYL-1402O is therapeutically equivalent to bevacizumab in combination with CP, based on ORR by both FDA and EMA requirements. They added that their results support extrapolation to all applicable conditions for bevacizumab, because bevacizumab “has the same mechanism of action across all indications and the dose used for NSCLC is highest among all approved indications.”

In December, Tot Biopharm said it has been granted regulatory approval for a bevacizumab biosimilar (Pusintin) by China’s National Medical Products Administration.

REFERENCE
Study: Cemiplimab Is More Cost-effective Than Chemotherapy for Some Patients With NSCLC

IN THE UNITED STATES, cemiplimab serves as a cost-effective option for first-line treatment of non–small cell lung cancer (NSCLC) in patients who are at least 50% PD-L1 positive, according to an analysis published in Clinical Oncology.

Until recently, platinum-doublet chemotherapy has been the only option for first-line treatment in patients with NSCLC negative for actionable molecular markers. However, researchers explained, advances in immunotherapy now offer an opportunity for new paradigms.

One potential alternative to chemotherapy is cemiplimab, “a recombinant human IgG4 monoclonal PD-1 antibody that blocks the interaction between PD-1 and PD-L1/PD-L2,” authors wrote. Results from the phase 3 EMPOWER-Lung 1 trial showed that cemiplimab resulted in improved overall survival compared with chemotherapy and was less likely to be associated with treatment-related adverse events of grade 3 or higher.

To better understand the financial burden of the novel anti–PD-1 treatment, investigators conducted a cost-effectiveness analysis using clinical data from the EMPOWER-Lung 1 trial.

“Patients with a tumor proportion score greater than 50% were randomly allocated to receive either cemiplimab 350 mg intravenously every 3 weeks for up to 108 weeks or 4 to 6 cycles of platinum-doublet chemotherapy, based on the trial,” authors wrote. Patients were also permitted to cross over if disease progression occurred following first-line treatment.

In their model, researchers presumed that 74% of those in the cemiplimab arm received chemotherapy, and that 23% in the chemotherapy group received cemiplimab, based on the data in the clinical trial.

Their decision tree and Markov model also included any AEs grade 3 or higher or those occurring at a frequency of 5% or greater. In addition, “the cost of each treatment arm consisted of the costs of drugs, drug administration, laboratory tests, radiographic imaging, follow-up appointments, treatment of AEs and terminal care,” while “a typical patient with a weight of 89 kg and body surface area of 1.84 m² was used to calculate dosage data for intravenous drug administration.”

Health outcomes were calculated as quality-adjusted life-years (QALYs) and cost-effectiveness was converted to incremental cost-effectiveness ratios (ICERs).

Analyses revealed:

- Over 20 years, treatment of NSCLC with cemiplimab yielded an extra 1.07 QALYs at an additional cost of $98,211 compared with chemotherapy.
- Cemiplimab treatment was associated with an ICER of $91,891/QALY and an incremental net health benefit of 0.087 QALYs at a willingness to pay (WTP) threshold of $100,000/QALY.
- The probabilistic sensitivity analysis indicated that cemiplimab provided an 83.2% probability of being cost-effective and that platinum-doublet chemotherapy had a 15.7% probability of cost-effectiveness.
- A 1-way sensitivity analysis suggested that the price of cemiplimab was the chief driver in this model.
- A subgroup analysis showed that cemiplimab was the preferred incremental net health benefit in more than half of the subgroups, including patients with squamous type disease and metastases.

The 1-way sensitivity analysis also showed that the hazard ratio for progression-free survival—with improved health mainly derived from a decreased risk of disease progression—served as the pivotal driving factor for ICER, authors explained.

Findings of the current analysis may not be generalizable to other countries, in part due to different WTP thresholds. However, “when considering WTP in middle-income regions, if the price of cemiplimab per 50 mg was set at less than $925, the ICER could be less than $30,000, suggesting that cemiplimab would also be cost-effective in those locations,” they said.

Results from the phase 3 EMPOWER-Lung 1 trial showed cemiplimab resulted in improved overall survival compared with chemotherapy and was less likely to be associated with treatment-related adverse events of grade 3 or higher. To better understand the financial burden of the novel anti–PD-1 treatment, investigators conducted a cost-effectiveness analysis using clinical data form the EMPOWER-Lung 1 trial.

The retrospective nature of data on survival and AEs used in this analysis marks a limitation, while additional research on the impact of different treatment regimens on individual quality of life is warranted.

Overall, “the present study shows that for advanced NSCLC with PD-L1 more than 50%, cemiplimab appears to be a more cost-effective treatment option than chemotherapy at the current WTP threshold of $100,000/QALY in the United States,” authors concluded.

“Meanwhile, health economics evaluations may provide an opportunity to aid the development of precision medicine depending on the individual characteristics of NSCLC patients.”

REFERENCE

CMS Seeks to Pass Part D Price Reductions to Beneficiaries

ON JANUARY 6, CMS PROPOSED a draft of rules aimed at transparency in Medicare Advantage (MA), including improvements for beneficiaries who are dual eligible, and changes to Part D, including passing any price concessions received from pharmaceutical firms to beneficiaries at the pharmacy counter.

“We are dedicated to ensuring [that] older Americans and those with disabilities who are served by the Medicare program have access to quality, affordable health care, including prescription drugs and therapies,” CMS Administrator Chiquita Brooks-LaSure said in a statement. “Today’s proposed actions follow our guiding principles by improving health equity and enhancing access to prescription medications.”

As described in a fact sheet, CMS wants Part D plans that have agreements with certain pharmacies, where they pay less for drugs if metrics are not met, to share the savings with beneficiaries by applying those savings to the negotiated price of the drug.
The agency also proposes redefining the negotiated price as the lowest admissible payment to a pharmacy, starting January 1, 2023.

In the proposed rule, CMS said costs paid by the Plan D would be reduced by 2%, or $21.3 billion, over 10 years. However, the plan would cost the government $40 billion during that time due to increases in direct subsidy and low-income premium subsidy payments, representing a 3% increase. Drug makers would save about $14.6 billion, CMS said.1,3

CMS said the move would “reduce beneficiaries’ Medicare Part D out-of-pocket costs and improve price transparency and market competition in the Part D program.”

For beneficiaries who qualify for both Medicare and Medicaid, CMS is looking to improve the information they receive in an effort aimed at health equity and reducing health disparities.

The proposed rule would require that MA organizations with Dual Eligible Special Needs Plans (D-SNPs) establish, maintain, and consult with 1 or more enrollee advisory committees to include the voices of these beneficiaries, who tend to have low income and more chronic illnesses. The proposal would streamline the grievance and appeals processes in certain D-SNPs, simplify information about accessing services, and change MA cost-sharing aimed at improving payments to providers who serve this population.

Beneficiaries would have to be asked about their barriers to accessing care through standardized questions in required health risk assessments on housing instability, food insecurity, and transportation. CMS would boost oversight of third-party marketing organizations that act, directly or indirectly, on behalf of MA organizations and Part D sponsors by requiring free translation services.

In addition, applications for new or expanded MA plans must show they have a sufficient network of contracted providers. If previous performance was poor, MA plans would not be able to expand.

Another part of the rule would increase what MA and Part D must report in their medical loss ratio (MLR). The MLR is the portion of premiums spent on medical care; currently, plans are required to meet an MLR of 85%.

The proposal would require the reporting of the underlying cost and revenue information needed to calculate and verify the MLR percentage and remittance amount, which was the case from 2014 to 2017.

In addition, if the rule is adopted, plans would have to include the amounts spent on providing supplemental benefits—dental, vision, hearing, transportation, and meals—which are not provided in traditional fee-for-service Medicare. •

CLN-081 functions by selectively targeting cells that express EGFR exon 20 insertion mutations while sparing cells expressing wild-type EGFR, according to a company statement. A phase 1/2 trial is underway to evaluate various doses in patients whose NSCLC has progressed on or after prior therapy.1

The designation, which serves to expedite the development and review of drugs intended to treat a serious condition, is based on updated phase 1/2a data showing that CLN-081 led to a high response rate and durable response among heavily pretreated patients.

Those data, which were released in December 2021, revealed that of the 36 patients enrolled in the 100-mg twice-daily cohort, 14 achieved a confirmed partial response, for a 39% confirmed response rate; the median duration of response was greater than 15 months. In the initial cohort of phase 1 patients (n = 13), median progression-free survival was 12 months.

When it comes to safety and tolerability, both diarrhea and rash have been limited to grade 1 and 2 events.

“We are extremely pleased that Cullinan has received breakthrough therapy designation from the FDA for CLN-081, a distinction that underscores the urgent need to bring improved targeted treatments to this patient population and further supports the differentiated clinical profile of CLN-081,” said Nadim Ahmed, CEO of Cullinan Oncology. 2

“We look forward to ongoing, productive regulatory discussions with the FDA, which are further enabled with this designation,” he added. •

REFERENCES

BIOMARKERS

Analysis Identifies Potential Biomarker of Frailty in Multiple Myeloma

NEUTROPHIL TO LYMPHOCYTE RATIO (NLR) could serve as a readily available potential biomarker of frailty among older adults with multiple myeloma (MM), according to research published in the Journal of Geriatric Oncology.

Specifically, NLR combines “a marker of inflammation (neutrophilia) and reduced cell turnover (lymphopenia) to reflect aging-related alterations in the immune system.”

Median patient age at MM diagnosis is 70 years, and in the next 15 years, it is expected that approximately 75% of new cases will be in patients aged more than 65 years. However, despite improving treatment options, outcomes are still suboptimal for this patient population as older adults continue to have high early mortality, excess treatment-related toxicity, and inferior survival, authors explained.

Frailty, defined as an “age-associated decline in reserve and function resulting in a reduced ability to cope with acute or external stressors faced every day,” is associated with poor outcomes among adults with MM. Although several methodologies of assessing frailty exist, restraints on time and resources have inhibited widespread adoption in routine clinical practice, researchers noted.

Previous research has indicated that NLR can predict survival and serve as a frailty marker among older individuals with and without cancer; however, its role in patients with MM remains unclear.

To better understand the potential use of NLR in MM, investigators assessed the association among pretreatment NLR, frailty, and overall survival using
data gleaned from the Flatiron Health electronic health record (EHR)–derived database. All patients included in the analysis had a diagnosis of MM between 2011 and 2020 and were aged at least 60 years at the time of diagnosis. Individuals also had records of pretreatment absolute neutrophil and lymphocyte counts up to 90 days before the start of first-line therapy, and they were followed until death or last date of last structured activity in the EHR. A total of 1729 individuals were included in the final analyses, with a mean (SD) age of 72 (6.7) years at MM diagnosis. Of these, a slim majority (52.8%) were male and 61% were non-Hispanic White. Researchers stratified calculated NLR values into quartiles (Q).

Authors found the following:

- Median NLR was 2.13 (interquartile range, 1.44-3.31).
- Of the 1135 patients with known frailty status, 55% met criteria for frailty.
- Multivariable analysis revealed 2.1-fold higher odds of frailty (95% CI, 1.42-3.10; P < .001) for patients in the NLR Q4 group vs the NLR Q1 group.
- In a multivariable analysis, adjusting for age, sex, race/ethnicity, M-protein type, stage, high-risk cytogenetics, baseline creatinine, lactate dehydrogenase, and type of first-line therapy, patients in the NLR Q4 group had a 1.51 times increased hazard of death (95% CI, 1.15-1.98; P = .002) compared with those in the NLR Q1 group.

“Because absolute neutrophil and lymphocyte counts are routinely obtained as a part of initial workup for MM, NLR represents an easily obtained potential biomarker for frailty that can help identify older adults with MM who are at risk of inferior outcomes and provide an opportunity for targeted interventions to mitigate this impact,” the authors concluded.

Inflammation has been put forward as one potential change that could be linked with frailty in older individuals, as proinflammatory cytokines could promote protein degradation or affect metabolic pathways.

More research is warranted on the association between NLR and survival in patients with MM and on older adults with MM in general. In the current analysis, frailty information could be ascertained only from those with complete data recorded in the EHR, marking a limitation. An underrepresentation of African Americans in this cohort was another limitation. “This is relevant because benign ethnic neuropenia is frequently seen among African Americans and the precise role of NLR in this population needs to be clarified,” researchers explained. •

**REFERENCE**


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**Molecular Profiling Locates Possible Prognostic Biomarker for Treatment Response in HNSCC**

**REAL-WORLD OVERALL SURVIVAL (OS)** among patients with oropharyngeal squamous cell carcinoma (OPSCC) and non-oropharyngeal (non-OP) head and neck squamous cell carcinoma (HNSCC) differed significantly based on the presence of the human papillomavirus (HPV) surrogate marker p16, with further implications identified regarding time on treatment with immune checkpoint blockade (ICB) therapies. Findings were published in Cancers.

Identified as the sixth most common cancer worldwide with incidence expected to increase by 32% in the next 2 decades, patients with recurrent and/or metastatic HNSCC typically have a poor prognosis. Although diagnosis of HNSCC is typically related to tobacco and alcohol use, incidence of HPV-associated HNSCC has risen substantially. Those positive for the virus whose HNSCC stems in the oropharynx have exhibited better survival outcomes. Researchers sought to further investigate the association of HPV and/or its surrogate marker p16 with response to standard-of-care ICB therapies in patients with OPSCC and non-OP HNSCC.

“We also investigated other potential biomarkers and mutations that may predict improved response to ICB in both HPV-positive and -negative patients with HNSCC,” they added.

“Patients registered in the Caris Life Sciences CODEai database with non-OP HNSCC and OPSCC were recruited and identified by comprehensive molecular profiling to be positive or negative for p16. In total, 2905 HNSCC cases were identified; 948 of these were OPSCC. Of those tested for both HPV and p16 directly, 32% (251/791) were p16-positive and 28% (91/326) were HPV-positive. Among patients with OPSCC, the most common mutation was TP53 (33%), followed by KMT2D (17%) and KMT2D (10.6%), in which TP53 mutations were more common in p16-negative (49%) vs p16-positive patients (10%; P < .0005).”

“Alignment with prior findings, real-world OS was found to be longer in p16-positive vs p16-negative patients with OPSCC (33.3 vs 19.1 months; HR, 0.597; P = .001). Real-world OS was also significantly longer in p16-positive vs p16-negative patients with non-OP HNSCC (34 vs 17 months; HR, 0.551; P = .0001). No difference in the time on treatment (TOT) was identified in ICB-treated patients with OPSCC who were p16-positive or -negative (4.2 vs 2.8 months; HR, 0.796; P = .221). Conversely, p16-positive patients with non-OP HNSCC treated with ICB exhibited higher TOT compared with the p16-negative group (4.3 vs 3.3 months; HR, 0.632; P = .016), which researchers say indicates that p16 may be used as a prognostic biomarker in non-OP disease. “In the future, these results may help guide treatment decisions and provide a rationale for further investigation. Clinical trials with large patient populations are required to assess whether p16 and other potential biomarkers can predict immune checkpoint blockade treatment response.”

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**REFERENCE**

PAYMENT MODELS

Alternative Payment Models Can Stabilize and Improve Practice Radiation Reimbursement
HOW VALUE-BASED CARE IS CHANGING RADIATION ONCOLOGY FOR THE BETTER

COURTNEY DEAN, MBA

CONTINUED FROM COVER

Additionally, 30% of all Medicare beneficiaries are slated to be in the Radiation Oncology Alternative Payment Model (RO APM), which despite ongoing delays is a looming threat to reimbursement; it is now scheduled to start in January 2023. Commercial payments are often tied to Medicare reimbursement, thus exacerbating declining reimbursement. Increased prior authorizations and complexity of care, declining referrals, and rising equipment costs compound the negative effects on managing a radiation oncology practice. Radiation oncology, according to the results of one study, had the highest risk of prior authorization, with administrative costs for authorization alone accounting for more than $40 million.1,4 ASTRO also reported that the majority of treatments subject to prior authorization are approved, yet they delay care for patients with cancer.

Practices can act today to gain some control over how these emerging trends will impact their viability and independence in the future. By developing value-based APMs for commercial payers, practices can employ reimbursement models that more accurately align incentives with the care provided while minimizing known and unknown threats to future reimbursement. Commercial radiation APMs are detailed contracts between practices and private payers that establish fixed payment rates per episode of care (EOC) based on historical rates and utilization, protecting against negative reimbursement pressure from changes in treatment patterns and Medicare code evaluation. Once a trusting relationship has been established between a payer and provider, discussions may also be possible concerning issues such as preferred provider status, patient steerage, and streamlined or eliminated prior authorizations. The ultimate goal is to align reimbursement with high-quality, patient-centric, guideline-based care.

To best prepare participating practices, The US Oncology Network (The Network), a large network of independent physicians dedicated to delivering value-based, integrated care to patients close to home, has developed radiation APM design options that fall into 2 categories: episode-based payments and capitation. The episode-based model is designed to be flexible, anchored by either a disease site– or stage–based or a modality-based framework. Some commercial payers may prefer one framework over the other based on the ability to implement and administer the payment model within the constraints of their claims system.

The disease site– or stage–based framework involves prospective payment for a defined, single EOC based on the patient’s disease site or stage. The most common disease sites treated with radiation—ie, prostate and breast cancer—are a good starting point for radiation case rates based on disease site. This option provides payers with predictability and protection against uncontrolled increases due to advanced technology adoption. The modality-based framework involves a prospective payment for a single EOC based on various radiation technologies, including 3-dimensional (3-D) conformal therapy, intensity-modulated radiation therapy, stereotactic radiosurgery/stereotactic body radiotherapy, and high-dose rate/low-dose rate brachytherapy. For example, a modality-based, 3-D conformal case rate would have a single payment regardless of what cancer type the patient has vs a disease site–based model that would have a single payment regardless of what type of technology was used to treat the patient. The modality-based model tends to capture a higher amount of the total radiation episodes with a fewer number of case rates, which payers and practices may find easier to administer.

In a capitation model, providers take on more financial risk because they are paid on a per-member per-month (PMPM) basis for all radiation services rendered to a certain payer population and not on an episode- or utilization-based reimbursement methodology. In this model, a practice should have sufficient capacity and scale to provide a commercial payer population with access to convenient and quality care in a defined geographic area. If a practice and payer have not historically partnered closely together in a market, starting with an episode-based model and moving to a capitation model in the future would be an appropriate glide path to build trust and the relationship between the payer and provider.

By developing value-based alternative payment models (APMs) for commercial payers, physicians can employ reimbursement models that more accurately align incentives with the care provided while minimizing known and unknown threats to future reimbursement. Commercial radiation APMs are detailed contracts between practices and private payers that establish fixed payment rates per episode of care (EOC) based on historical rates and utilization, protecting against negative reimbursement pressure from changes in treatment patterns and Medicare code evaluation.

Both radiation payment models provide a payer with predictable spend and enhanced value based on shared financial risk with the practice in the form of defined case rates or a PMPM model. The models are built to reward the combination of cost efficiencies and quality outcomes. They allow physicians to practice medicine while encouraging treatment optimization by adhering to evidence-based clinical pathways. Payers can provide value to the provider through these models by incorporating steerage and reducing administrative burden on practices by eliminating prior authorization for radiation services. Payers can explore technologies, tools, and analytics to reduce paperwork and redundancy, and to enhance communication with providers. Many practices in The Network have found that value is created for patients with more prompt access to care, with a streamlined billing process that allows for paying out-of-pocket expenses on
one bill or explanation of benefits, vs the continuous fees applied and collected as part of a fee-for-service model.

New York Oncology Hematology (NYOH), a practice in The Network, offers an excellent case study in how to develop and expand RO APMs. In 2016, NYOH started slowly with its new commercial APM, pitching the concept to 1 payer, a large insurer in the Albany market that provides Managed Medicare, Medicaid, and Marketplace plans, representing 7% of the NYOH payer mix. Negotiations lasted a year, and by the end of 2017, the new APM was up and running smoothly.

The successful pilot provided proof of concept, demonstrating financial stability for the practice and an enhanced experience for the patient, and gave NYOH confidence to move forward with other payers. Next, the practice began negotiations with a large New York nonprofit insurer that represented 32% of the NYOH payer mix. Discussions lasted just 10 months, with new radiation case rates taking effect in January 2019. Currently, NYOH is working to expand the pilot payer agreement to cover additional disease sites under the case rate model, in addition to renewing and extending their second commercial payer case rate agreement.

Looking back at how success was achieved, NYOH identified several crucial activities that will help other practices transition to the new APM payment methodology. To begin, they established 1 successful case rate pilot to demonstrate proof of concept and patient, physician, and payer benefits. To maintain a high visibility of case rate performance, radiation leadership continuously monitored and presented the results to practice leadership. Another factor leading to success was having a key radiation oncologist champion the radiation APM strategy within the practice. Early alignment of key stakeholders on processes to match practice and payer capabilities was instrumental in success.

“NYOH is thrilled with the implementation and outcomes associated with our case rate agreements. They have stabilized costs of care and reimbursement to the practice all while lowering the out-of-pocket costs for the patient,” explained Todd Doyle, MD, a radiation oncologist at NYOH. “We show payers high-quality care with adherence to evidence-based pathways, and we simultaneously receive reduced administrative burdens with ‘gold carding.’ We are free to just be doctors again.”

Moving to a whole new way of doing business was not easy, and there were obstacles to overcome. NYOH succeeded by identifying the problems that they were encountering and promptly developing concise strategies to overcome them. To ensure that all practice leadership understood the radiation APM strategy, monthly reporting of case rate performance compared with fee-for-service was done, demonstrating that performance was on target while educating leadership on the financial benefits. Operational changes were essential to successfully administer radiation case rate methodology. Operational playbooks were created and monitored until new behavior patterns were firmly established. In some instances, payers could have trouble implementing APMs due to their own administrative challenges. To overcome this obstacle, practices and payers worked collaboratively to resolve administrative limitations and establish modality-based case rates.

CMS will launch the RO APM, an example of a disease site–based framework. The RO APM is designed to test an APM in radiation oncology for a 5-year measurement period, which is now set to begin on January 1, 2023. Participation in the RO APM is mandatory for both physician group practices and hospital outpatient departments practicing in randomly selected zip codes across the country. Key aspects of the model include site-neutral, prospective, disease site–based EOC payments in addition to clinical and quality reporting metrics and performance measurement. The model will test whether the APM will lower cost for Medicare, while preserving or improving quality of care for Medicare patients. Episode-based payments will be based on national base rates, trend factors, and adjustments for each RO participant’s case-mix, historical experience, and geographic location. The bundled payment amounts will be reduced in the form of a fixed discount factor set by CMS. Additional withhold will be applied for incorrect payments and quality and patient experience, which the practice can earn back through quality measure reporting and performance outcomes.

The Network will have 13 practices participating in the RO APM starting in 2023. Because this is a mandatory, government-controlled program, »

### CLINICAL PATHWAYS

**ASTRO Offers Guidance on EBRT for Primary Liver Cancers**

By EBO Staff

**THE AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)** has released a guideline on the use of radiation therapy to treat adult patients with primary liver cancers using external beam radiation therapy (EBRT). Evidence-based recommendations in the guideline outline indications and optimal EBRT dosing, techniques, and treatment planning for patients with hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHC), with a strong emphasis on multidisciplinary care. EBRT aims high doses of targeted radiation at tumor sites from outside the body with noninvasive techniques and, in some cases, has been underutilized in treatment where it could be effective.

The EBRT guideline, ASTRO’s first for primary liver cancers, was published in the January issue of **Practical Radiation Oncology.** It was based on a systemic literature review of articles published from January 2000 through February 2020.

Primary liver cancers are among the most commonly diagnosed types of cancer and the fourth leading cause of cancer death worldwide. Incidence rates in the United States have more than tripled since 1980, rising approximately 2% each year in the past 2 decades, according to the American Cancer Society. An estimated 42,230 new cases were diagnosed last year. Mortality rates from HCC and IHC also continue to rise, despite the growing availability of screening for HCC and improved prevention and treatment of diseases that lead to liver cancer (ie, hepatitis B, hepatitis C, nonalcoholic fatty liver disease).

“Patients diagnosed with liver cancer often have a number of treatment options available to them, and they should be presented with each of them before a treatment course is decided. The different disciplines—hepatology, surgical oncology, interventional radiology, and radiation oncology—should all be involved in multidisciplinary treatment discussions to determine what might be best for each patient,” said Smith Apisarnthanarax, MD, vice chair of the guideline task force, medical director of the Seattle Cancer Care Alliance, and professor of radiation oncology at the University of Washington in Seattle. “We feel this guideline is an important milestone in the management of primary liver cancers, as we hope to provide practitioners and the public with a systematic and evidence-based foundation of where EBRT might fit into the overall complex picture of treating these challenging cases.”

Patients with liver cancer typically have multiple comorbidities, which can complicate diagnosis, staging, and treatment decision-making. Among the key considerations is whether a patient has underlying cirrhosis, which is present in approximately 90% of patients with HCC.

For patients whose primary HCC is confined to the liver, treatment options can include a liver transplant, tumor removal through surgery, thermal ablation, and catheter-based therapies. If cancer is advanced, patients and clinicians can consider systemic therapy, including targeted therapy and/or immunotherapy. For IHC, standard treatment includes a combination of surgery and chemotherapy with or without radiation. A study presented at the 2021 ASTRO Annual Meeting found that just 4% of eligible patients received EBRT as a bridging therapy before liver transplant.
PAYMENT MODELS

Continued from previous page

“Historically, low utilization rates for external beam radiation were due to technological limitations that made it challenging to avoid healthy liver tissue. However, with significant advances in imaging and radiation treatment delivery over the past 15 years and improved understanding of how the liver responds to radiation, we now have an increasing amount of clinical data on the role that EBRT can play for patients with these diseases,” said Higinia Cardenes, MD, PhD, chair of the guideline task force and a professor of clinical radiation oncology at Weill Cornell Medicine in New York, New York.

Recommendations cover patient selection, planning and delivery techniques for EBRT in various clinical situations, and palliative treatment settings. Key recommendations include the following:

- A potential first-line treatment for patients with HCC confined to the liver who are not candidates for curative therapy.
- A consolidative therapy for patients with incomplete responses to other liver-directed treatments.
- A salvage therapy option for patients with local recurrences after other treatment.

In addition, EBRT is conditionally recommended in the following circumstances:

- For patients with multifocal or unresectable HCC confined to the liver.
- For patients with macrovascular invasion, when sequenced with systemic or catheter-based therapies. The guideline features treatment algorithm to manage HCC contained in liver and for HCC with macrovascular invasion.
- In the palliative setting for symptomatic primary HCC and/or HCC that has invaded a blood vessel.
- As a bridging therapy prior to liver transplant or before surgery in select patients.

Other recommendations include the following:

- EBRT should be considered for patients with unresectable IHC, with or without chemotherapy, typically after systemic therapy. For patients with resected IHC and high-risk features, adjuvant EBRT is conditionally recommended.
- Treatment algorithms are provided.
- The guideline addresses optimal dosing, fractionation, treatment planning and delivery techniques, and calls for individualized care that considers the location of the tumor and how advanced the cancer is, as well as liver function.

We anticipate many challenges when implementing the RO APM that will cause administrative complexities and increase operational costs. These include:

- **DETERMINING ELIGIBILITY AND TIMING** of the EOC start for those patients who are included in the model will be a challenge, as not all locations and patients are included in the model.
- **COLLECTING AND SUBMITTING QUALITY MEASURES** and clinical data elements will be a time-consuming, manual process at the beginning, as vendors refine offerings to streamline these processes.
- **REVENUE CYCLE CHALLENGES** are expected, as we work through split payment billing and coordinating payment with secondary payers. In commercial models, these challenges should be overcome prior to model implementation.

We do expect that participating practices in The Network will build valuable experience through participation in the RO APM that will help prepare them for future success in value-based care models in oncology.

Over the years, The Network has cultivated key learnings through experience with developing and implementing radiation APMs at practices across the country. We have learned that radiation APM contracts can be successfully negotiated and administered by community practices. The Network currently supports more than 25 radiation APMs. We have proven that APMs can stabilize or improve practice radiation reimbursement, and we have found that exclusivity, preferred provider status, or elimination of prior authorization requirements adds significant value under radiation APM contracts.

The Network has experienced recent wins and is in the process of continuing to expand its radiation APM footprint. In 2020, Minnesota Oncology entered their first radiation APM contract, a disease site-based case rate with Blue Cross Blue Shield of Minnesota. More recently, additional Network practices in Maryland and Ohio are planning to finalize their first radiation APM contracts with commercial payers in early 2022.

The US Oncology Network has shown that radiation APMs can fulfill our goal of aligning payment to improved patient care while reducing administrative burden. Physicians, practices, and payers find value in these models, while patients receive guideline-based therapy without unnecessary delays. Developing APMs can be daunting, but with time, expertise is developed to make more rapid deployment of these models easier. We will continue to work with payers and practices to continually enhance development of radiation APMs.

**Author Information.** Courtney Dean, MBA, is managed care contracting regional director for The US Oncology Network.

**References**


New Drug Combo May Improve Outcomes in Unresectable Liver Cancer
Read more at: https://bit.ly/31JaZH2
A NEW SURVEY OF ONCOLOGY PRACTICES finds that those participating in the Oncology Care Model (OCM), CMS’ alternative payment model (APM) in cancer care, say that the program has succeeded in reducing costs and improving patient outcomes. But with the APM set to expire June 30, 2022, and no successor on the horizon, respondents to a survey released January 31, 2022, by the Community Oncology Alliance (COA) say some of the program’s most popular and successful features—such as dedicated navigators and weekend appointments—could be reduced or lost if revenues that supported them are eliminated.

CMS’ Center for Medicare and Medicaid Innovation (CMMI) launched the OCM in 2016 to run over 5 years, giving participating practices tools and funds to reinvent cancer care delivery with an emphasis on coordinating care, preventing unnecessary trips to the emergency room, offering survivorship care, and managing the cost of therapies. The program was originally set to run through 2021 but was extended a year due to the pandemic.

A key feature of the program is the Monthly Enhanced Oncology Services (MEOS) payment, which funds the extra services practices offer under the program. This payment is triggered by each cancer episode at the practice, while other funds under the program involve more extensive reporting requirements.

Of the 126 practices that were still participating in the OCM in July 2021, 83 responded to COA’s survey: 78 had participated in the OCM and 73 were still participating. The results reported by COA reflect feedback of the 51 practices that completed the entire survey. Those participants were asked how the OCM impacted cancer care, whether they would continue in the model, and whether they expected reductions in service when the model ends.

In other analyses of the OCM, the initiative has received high marks for improving patient experience, but practices needed time to learn to fully implement the model. As the rise of immunotherapy unfolded during the model’s implementation, practices struggled to make the financial savings pieces work, since pricing assumptions often failed to keep pace with cancer innovation. Still, many oncologists say they would not want to revert to delivering care without navigators, care planning, or survivorship services, and many larger practices have taken steps to figure out how to offer these services post-OCM.

In interviews for the December 2021 issue of Evidence-Based Oncology (EBO), experts said the concern is that without the financial support in the form of MEOS payments were reduced or eliminated.

STRONG IMPACT ON PATIENT EXPERIENCE. Respondents to the COA survey were asked to use a scale of 0-100, with 0 having no impact and 100 having a tremendous impact, to evaluate the OCM in 5 categories: patient experience, operational efficiencies, consistency in cancer treatments, reduced total cost of care, and addressing health disparities.

Average responses for all categories are reported here, showing the OCM has had positive impact: patient experience, 62; operational efficiencies, 56; consistency on cancer treatment, 56; reduced total cost of care, 49; addressing disparities, 45.

FUTURE OF MEOS PAYMENTS IS KEY. The survey asked practices if they would continue in the OCM, and whether that view would change if financial support in the form of MEOS payments were reduced or eliminated:

- 84% said they wanted to continue in the OCM as it is currently operating, with full MEOS payments.
- 80% said they would continue, even if MEOS payments were reduced by half.
- 27% would be willing to stay in the OCM without any MEOS payments.

Practices were given the chance to give open-ended comments on what the end of the OCM would mean to patients. Many said that staff now considered an essential part of the care routine would be reassigned or lost; some offered examples, such as reassignments for lay navigators or program coordinators, or the end of weekend hours that help prevent overuse of the emergency department.

When asked about service reductions due of the end of the OCM, the average response said practices could reduce key positions like care planner, survivorship planner, and nurse navigator by roughly 25%.

SURVEY PARTICIPANTS WANT AN OCM SUCCESSOR. The survey participants expressed disappointment that CMMI has no plans for a successor model to OCM in place. In 2019, a plan called Oncology Care First was proposed, but it was delayed due to the pandemic, and its future is unknown.

CMMI has a duty to shepherd ongoing oncology reform, given the investment practices have made, according to Bo Gamble, CMS Director of Strategic Practice Initiatives. “The OCM led the way for a transformation in the delivery of cancer care, as well as a mindset for continual quality improvement with emphasis on efficiency and value. There will be a void in leadership if CMMI steps away from this important work.”

COA President Kashyap Patel, MD, CEO of leading OCM participant Carolina Blood and Cancer Care Associates in Rock Hill, South Carolina, urged CMMI to help community oncology practices continue the progress made under the OCM, not halt it.

“Practices have poured time and resources into this important project with a clear benefit to patients,” said Patel, who is also the associate editor of EBO. “CMMI should be thinking of ways to use the lessons learned from the OCM going forward, not ending it without a plan for the future.”

REFERENCES

MARY CAFFREY
Telehealth at Minnesota Oncology: Tackling COVID-19, Educating Patients, and Overcoming the Weather

MARY CAFFREY

CONTINUED FROM COVER

Rajini Katipamula-Malisetti, MD, a medical oncologist and hematologist with Minnesota Oncology who practices in Coon Rapids, has seen telehealth’s usefulness up close. She spoke with Evidence-Based Oncology in December 2021, as the Omicron variant fueled another surge of COVID-19 cases and triggered another rise in hospitalizations. This happened as Minnesota reached the season when, in prior years, a wintry blast could wipe out an entire day’s schedule.

But now, schedulers at Minnesota Oncology know that if patients call to say they can’t come because of a snowstorm, there’s a solution. “We’re just asking them to offer telehealth appointments,” Katipamula-Malisetti said. “We don’t want to cancel appointments.” Better yet, the team can look at the forecast and proactively switch patients to telehealth appointments if a storm is coming. “It’s been really helpful,” she said.

Katipamula-Malisetti, a recipient of the ASCO Merit Award for her research on trends in mastectomy rates and MRI, is a believer in giving her patients a thorough education on what will happen during cancer treatment. She has found that with the pandemic, telehealth is a valuable tool that also offers some unexpected benefits.

Solving Multiple COVID-19 Challenges

Having patients see their physician, social worker, or nutritionist via telehealth obviously reduces the opportunity for infection, but that’s not the only problem it solves, Katipamula-Malisetti said. Staffing shortages have emerged across health care, and Minnesota Oncology may not have staff at each clinic for every type of service. Telehealth helps address that: “There are certain specialties where we’re still leveraging telehealth significantly,” she said.

Examples include the initial survivorship visit, at which patients and caregivers receive information about the effects of chemotherapy so that everyone knows what to expect. Due to COVID-19, right now telehealth can be a better option for this visit, she said. “We still have a 1-visitor policy, whereas with telehealth, we’re able to have a patient’s daughter and her husband or whoever is going to be the point person. So, we’re still trying to have those survivorship visits be telehealth visits,” Katipamula-Malisetti said.

Another example: a genetics session at which family history is taken—having multiple family members participate is a plus, she said. Depending on the practice or the insurer, telehealth was used for these visits even before the pandemic due to the relative scarcity of certified genetic counselors. She cited visits about nutrition as a third example.

Due to COVID-19, Katipamula-Malisetti said, patients are more willing to try telehealth than they might have been in the past. With staffing shortages and hospital overcrowding, the challenge to simply gain access to care makes telehealth a viable option. For those who might not have tried it before, “it’s worth a shot,” she said.

Reimbursement

So far, Minnesota Oncology has had a good experience with telehealth reimbursement for the types of appointments it schedules, Katipamula-Malisetti said. But she has heard about CMS paying less for visits if they are telephone only—in contrast with the early days of the pandemic, when the priority was to reach patients in any way possible. In her view, flexibility is important to address disparities until solutions to disparities are found.

Asked if telehealth could help gather patient-reported outcomes if gene- and cell-based therapies were to reach more patients, especially those in rural areas, she said that this would be useful. “I think this is a tool that we can really leverage,” she said. If patients need check-in every day or 2, using telehealth to gather information could be better for the patient and keep costs down, she explained. The same would be true for gathering data from clinical trials.

The ASCO Telehealth Survey

The Minnesota Oncology experience with telehealth generally aligns with survey results reported at the most recent ASCO meeting, in May 2021. Only 3 types of visits were found appropriate for telehealth by more than 50% of the providers: discussions of imaging or laboratory results, chemotherapy education, and genetics counseling. More than 50% of survivors found visits on imaging or laboratory results or financial counseling to be appropriate; 90% of providers thought financial counseling was appropriate within the context of a broader visit on supportive care. Follow-up care found appropriate for telehealth by more than 50% of both providers and survivors included symptom management; for survivorship care, more than 50% of providers and survivors endorsed nutrition consultations and patient navigation via telehealth.

For all the positives that telehealth can offer, the question of whether all patients have the same access to technology has lingered since the start of the pandemic. The ASCO survey results showed that among survivors, 2.5% reported having no phone or no smartphone, 6.7% reported no or unreliable broadband or internet access, and 10.9% reported being uncomfortable using technology.

Katipamula-Malisetti said she would like to see payers get involved with helping ensure equal access to telehealth for oncology care, perhaps through pharmacies. A single primary care clinic may be “inundated,” she said. But partnering with the local health care infrastructure through pharmacies would be an appropriate role for payers, she said. A small area of the pharmacy could be set up with a laptop for telehealth visits to accommodate patients who don’t own a computer or who lack sufficient internet service.

“Is there a way to move the needle?” she asked.

REFERENCES


With Approval for Axi-cel in Second-line on the Horizon, CAR T-Cell Therapy Poised to Enter New Phase

MARY CAFFREY

CONTINUED FROM COVER

Tisagenlecleucel (tisa-cel; Kymriah; Novartis) was approved in August 2017 for treating patients with pediatric acute lymphoblastic leukemia (ALL).1 Two months later came the approval of axicabtagene ciloleucel (axi-cel; Yescarta; Gilead/Kite Pharma) for treating patients with relapsed or refractory large B-cell lymphoma (LBCL).2 Both anti-CD19 treatments were approved for patients who had received at least 2 prior lines of therapy. By definition, these were very sick patients, and often their aggressive cancers meant there was little time to waste. But when CAR T-cell therapy first moved from clinical trials and into the real-world setting, the medical miracle collided with reality: those early days were rife with stories of frustrating delays as payers and institutions alike worked to get treatments approved before patients’ health deteriorated.

CAR T-cell therapy represented something new for patients and clinicians—and it was new to the reimbursement infrastructure as well. The cost of 1-time treatments was so high—$475,000 for tisa-cel and $373,000 for axi-cel—and the financial risk to hospitals so great, that in early 2018 a revenue cycle manager told Evidence-Based Oncology (EBO)6 each case required decision-making at the highest levels of his institution, a situation he hoped would “lessen over time.”

The lessons of that learning curve remain fresh as Kite Pharma prepares for a major milestone. The FDA will soon act on its supplemental biologicals license application for use of axi-cel as second-line therapy in relapsed or refractory LBCL. A target action date is set for April 1, 2022.2 This follows the results of the ZUMA-7 trial presented in December 2021 at the American Society of Hematology Meeting & Exposition (ASH). Lead investigator Frederick L. Locke, MD, of Moffitt Cancer Center in Tampa, Florida, showed that axi-cel quadrupled event-free survival (EFS) compared with the current standard of care (SOC), which includes high-dose therapy and autologous stem-cell transplant (ASCT).4 Approval of axi-cel for patients with LBCL who had failed only 1 therapy would potentially boost the number of patients eligible for axi-cel treatment by 11,000 just in the United States, according to data compiled by Kite Pharma (email to EBO).5 Kite Pharma CEO Christi Shaw has said the number of patients eligible for the treatment would roughly double, and Shaw and others from Kite Pharma say they expect the number of patients treated in second line to rise gradually, the same way the uptake of CAR T-cell therapy in third-line treatment increased over time.5,7

Alex Herrera, MD, a hematologist-oncologist at City of Hope in Duarte, California, who introduced Locke’s presentation at ASH 2021, noted that phase 3 findings from the TRANSFORM trial showed significant second-line benefits in LBCL from the CAR T-cell therapy lisocabtagene maraleucel (liso-cel; Breyanzi, Bristol Myers Squibb). The study results showed that liso-cel produced a risk reduction of 65% in EFS compared with SOC.8

Taken together, “The studies do suggest that CAR T-cells likely have a role as a second-line therapy,” he said in an interview. In both studies, patients receiving CAR T-cells had better outcomes, and there were better patient-reported outcomes.

“The hope, as a treating physician, is that we will be able to use these exciting therapies for our patients with primary refractory or early relapsed aggressive B-cell lymphoma to improve outcomes and their quality of life,” Herrera said.

Is the Health System Ready for CAR T in the Second Line?

From Kite Pharma’s perspective, progress in manufacturing, payer relations, and collaboration with the 111 institutions that administer axi-cel puts the CAR T landscape light years ahead of where it was in 2018. Some cancer centers are described by Kite officials as “well-oiled machines” when it comes to CAR T-cell therapy administration.

However, commercial payers and Medicare are not the same. Although Medicare reimbursement has improved since 2018, a gap remains between what CAR T-cell therapy costs and what Medicare pays. How institutions will address this as a new category of patients seeks CAR T-cell therapy remains to be seen.

An Avalere Health analysis of Medicare’s most recent reimbursement update discusses a change that puts CAR T-cell therapy and other immunotherapies in the same Medicare Severity Diagnosis Related Group (MS-DRG), which the analysis authors say could have dramatic effects at some hospitals.9

EBO™ spoke with Kite Pharma’s Robert Shelley, vice president for global market access and pricing, and Mary Lynn Carver, vice president and global head of public affairs. They highlighted items they say point to a smoother uptake for axi-cel in second-line treatment:

• Despite the projected increase in the number of patients being treated with axi-cel, the number of institutions administering the treatments will not rise sharply; these cancer centers are now experienced in the reimbursement process.

• Kite Pharma has published medical policies with 91% of US commercial payers; some policies are not published but access is confirmed.

• Kite Pharma’s experience with its second CAR T-cell therapy, brexucabtagene autoleucel (Tecartus), approved in 2020 for mantle cell lymphoma and in October 2021 for relapsed or refractory B-cell precursor ALL, shows that payers can rapidly incorporate new CAR T-cell therapy indications.10 In the ALL indication, “we achieved over 85% of commercial coverage within the first quarter of launch,” Shelley said.

• Investments in the manufacturing process—including a new facility—will keep turnaround times down even as the number of patients receiving axi-cel grows.

Of course, Shelley said, snags do occur. Coding errors happen, and occasionally a new employee at a health plan is unfamiliar with CAR T-cell therapy. And although the process may be easier than it was in 2018, one thing is the same. For commercial plans, “the reimbursement pathway to get funding for treating these patients is often under a single-case agreement,” Shelley said.

Will this change as axi-cel and eventually other CAR T-cell therapies are approved in second- or even first-line treatment? Shelley said there’s been discussion of this happening, but it’s challenging from both sides. These are still patients with rare diseases, he said.

“In 2022, do I expect to see a move to global case rates from the payer community? Probably not,” Shelley said. “As we move toward 2023? Perhaps, as we start to see some of the national payers moving in that direction—because the price of CAR T is well-known at this point.”

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Medicare Reimbursement Improves, Still Falls Short

From the beginning, the biggest questions institutions had about CAR T-reimbursement involved Medicare. Would they get paid? How much? And how long would payment take? The cancer centers that had run clinical trials in tisa-cel and axi-cel—and were thus best equipped to treat patients after approval—winced at the losses that accumulated as Medicare payments came in far below total costs, which for some patients could reach $1 million once hospital costs were included.11 Medicare's opening act with CAR T was a bust: CMS' early "pay for performance" agreement with Novartis for tisa-cel, in which the manufacturer would be paid only if the treatment worked within a month, was quickly withdrawn over ethics concerns, and the long journey to a national coverage determination began. Any progress individual states were making with regional Medicare Administrative Contractors was halted. In the interim, Medicare's billing framework was not set up to deal with something such as CAR T-cell therapy, so CMS defaulted to the MS-DRG for bone marrow transplant, which paid just $43,094.12-14 Although Medicaid covered a fraction of eligible patients, some states refused to cover CAR T-cell therapy at all.9,10 Since then, changes to the Medicaid Best Price rule and value-based reforms from CMS could make it easier for Medicaid to pay for these treatments.

In March 2019, Locke, who was a coauthor on the pivotal ZUMA-1 trial, told an audience at the National Comprehensive Cancer Network Annual Conference that what Medicare was paying providers for CAR T-cell therapy was not sustainable. "If it's not figured out soon, we will not be able to do this for Medicare patients," he said.13 By fiscal year (FY) 2021, CMS created an MS-DRG for CAR T-cell therapy, raised the average national reimbursement base rate to $239,933, and incorporated the use of add-on and outlier payments to bring Medicare's total payment closer to list prices. But a gap remained, and Avalere Health projected the FY 2022 reimbursement update will cause the net loss to widen again, to $30,988, even though base rates rose to $246,958.15

What's more, the FY 2022 changes under the Inpatient Prospective Payment System final rule adds new procedures codes under the MS-DRG and expanded the category from CAR T-cell therapy to "Chimeric Antigen Receptor (CAR) T-Cell and Other Immunotherapies."

The update was seen by some as a sign of CMS' flexibility toward new therapies, but Avalere Health warned in its analysis that "the financial impact of these changes will vary by hospital and in some cases may continue to fall short of fully recognizing provider costs of treatment."9 The ongoing gap, the authors wrote, "sometimes fails to cover total hospital costs, with potential negative impacts on provider uptake and patient access."

Long-term Survival Data Are Strong

When it works, CAR T-cell therapy seems like something from a science fiction novel: a treatment manufactured with a patient's T cells is infused back into the body to harness the immune system in the fight against cancer. Not long after its approval, there were discussions about whether giving CAR T-cell therapy earlier—when patients had not received as much therapy—would improve the success rates.16 Axi-cel, now approved for third-line treatment of follicular lymphoma, will likely be the first of several CAR T-cell therapies approved for use in second-line treatment. In addition to the liso-cel findings, results at ASH 2021 covered CAR T-cell therapies in multiple myeloma, such as additional phase 2 data for cilta-cabtagene autoleucel (cilta-cel) that showed strong responses when used in second-line treatment.17

Payers' initial hesitancy toward CAR T-cell therapy concerned its lack of a track record, given the cost. But as long-term data have come in, CAR T-cell therapy has outperformed other available options in overall survival.

The difficulty of getting patients to transplant may prevent some physicians from even referring patients for the procedure. If axi-cel is approved in the second line, one task will be educating physicians that most eligible patients successfully complete the chimeric antigen receptor T-cell procedure; the hope is that more doctors will be willing to refer their patients.

Besides the EFS data from ZUMA-7, patients who took axi-cel were also 2.5 times more likely to be alive after 2 years without the need for additional treatment than those who received SOC (40.5% vs 16.3%).5 Meanwhile, data published in October 2021 found that patients in ZUMA-1 had a 2-year survival rate of 54%, compared with 20% for patients enrolled in SCHOLAR-1, which was a retrospective study of similar patients treated with salvage chemotherapy.16 In his presentation at ASH 2021, Locke highlighted another important point taken from the ZUMA-7 data. Of the patients randomized to axi-cel, 94% successfully received CAR T-cell treatment; in comparison, only 36% of those randomized to SOC received high-dose therapy and ASCT.

This aspect of comparing axi-cel with ASCT is often overlooked, Carver said. The difficulty of getting patients to transplant may prevent some physicians from even referring patients for the procedure. If axi-cel is approved in the second line, one task will be educating physicians that most eligible patients successfully complete the CAR T-cell procedure; the hope is that more doctors will be willing to refer their patients. "That's a paradigm shift," she said. "We really have to work with referring physicians to make sure that they understand this." Herrera said the fact that so many patients never make it to transplant has been "a huge problem."

From the patient's perspective, he said, "Imagine having this option that you're striving for (transplant)—that, until recently, was the main curative treatment that we had for relapsed or refractory aggressive B-cell lymphoma. Except that we can't get you there most of the time. That's pretty tough." "So, if a much higher proportion of patients are going to be able to get CAR T-cells than arrive at transplant, from the perspective of the patient, I can only imagine that at least patients feel like they've got that shot—they were able to have a potentially definitive therapy to cure the disease."

Because some patients who had ASCT in second-line later need CAR T-cell therapy, the hope is that by offering CAR T-cell therapy first, the toxicity of ASCT is thus avoided. (Conversely, some patients who have CAR T-cell therapy in second-line may relapse and need further treatment, and ASCT might be an option). Shelley said health economics research is under way to explore the financial impact of all these possible outcomes.

Manufacturing and Time to Infusion Are Keys to Success

During December's ASH meeting, Michael R. Bishop, MD, director of the hematopoietic stem cell transplantation program at the University of Chicago presented findings from the phase 3 BELINDA trial, which tested the effectiveness of tisa-cel in second-line treatment. Unlike ZUMA-7 and TRANSFORM, the BELINDA study did not meet its end point. In a news briefing, Bishop said that although there were other differences between the 2 trials, he believed a key advantage for ZUMA-7 was the time to infusion was much shorter than in BELINDA—a median time of 27 days vs 52 days, respectively.19,20

Time to infusion is how long it takes for a patient's cells to be removed from their body through leukapheresis, brought to a manufacturing facility and transformed into the lifesaving treatment, and finally infused back into the patient. In ZUMA-7, patients did not have any bridging therapy, only steroids—which could be another reason the results differed from BELINDA. Once a patient is identified as a candidate for CAR T-cell therapy, any delays—whether due to manufacturing, scheduling, or trying to get approval from a payer—give the aggressive lymphoma time to advance.

Herrera said there could be many factors that go into a decision to give chemotherapy ahead of CAR T-cell therapy. "A lot of patients get bridging chemotherapy before they get their CAR T cells, and that's going to remain a reality," he said. But Herrera agreed that delays can cause problems—there was a recent stretch when patients experienced scheduling delays for leukapheresis, although it has improved recently. "That really puts us in a bind," he said.

City of Hope has made significant investments in CAR T-cell therapy administration, Herrera said, and he doesn't find payer coverage a "limiting issue." He agrees that production is "a critical factor" and the availability of manufacturing slots is very important. "This is an aggressive disease, and it can be difficult to control. If you have to wait several weeks just to get a collection, and then several weeks
to have production—that can be a real challenge. And it’s going to result in patients needing to get chemotherapy.”

This is where CAR-T cell therapy is unlike taking a pill or having a traditional infusion—is this a process, so finding efficiencies in that process will be key to improving patients’ chances of survival along with better science. Carver said with this in mind, Kite Pharma has built a 279,000 square foot manufacturing plant in Frederick County, Maryland, which is scheduled to be fully operational not long after the April 1, 2022, target date for axi-cel’s indication in second-line treatment.

At Kite Pharma, Carver said, “there’s a great deal of [research and development] in CAR T related to manufacturing, in the quality of the manufacturing and the quality of the T cells themselves. We’ve been doing a lot in automation...and our turnaround is very good—it’s in best in class in the industry.”

Still, Carver said, Kite Pharma continues to try to make the process even faster. “The automation that’s coming online in Maryland will help that,” he said.

In 2019, the Baltimore Business Journal reported that Kite Pharma’s expenditures on the Maryland project would be $85 million.25 But if the investment pays off, one analyst estimates the second-line indication for axi-cel could be worth $1.5 billion, according to Fierce Pharma.26

Engaging Payers at the Start

Shelley said Kite Pharma has been preparing for ZUMA-7 and the growth in the patient population for several years. “We’ve staffed up appropriately on a number of support functions with care managers [who] work with our hospital network to facilitate payer coverage. And we’ve strengthened our pharmacy coverage. Am J Manag Care 2018;24(11):OP05.


The question, Herrera said, is, “What’s the next step? Is it as consolidation after frontline therapy for patients who aren’t in a complete molecular response according to minimal residual disease testing? Or will we identify a population where we can attempt CAR T-cell therapy as a frontline therapy?”

In ZUMA-12, he said, patients in the study exhibited chemoresistance before they were given axi-cel. “Is there a group of patients we can identify who should be getting this as first-line therapy? I think that remains to be seen,” Herrera said, “but I anticipate that these questions are going to be asked.”

REFERENCES


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