POLICY

Considerations to Increase Rates of Breast Cancer Screening Across Populations

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**Author:** Nathan Markward, PhD, MPH; Milena Sullivan, MA; Blair Burnett, BA; Brook Getachew, BA; and Crystal Harris, MPH

**Introduction**

Routine screenings for breast cancer have the potential to detect disease at its earliest stages, when it is most amenable to treatment. If screenings are delayed or missed, the risk of later-stage diagnoses and initial presentation of more complex disease increases. The US Preventive Services Task Force (USPSTF), an independent regulatory panel that provides evidence-based guidelines for clinical preventive services, has recommended screenings for 4 types of cancer—breast, colorectal, cervical, and lung—among people who satisfy established age criteria and/or have certain risk factors. Currently, mammograms are recommended once every 24 months for women aged 50 to 74 years. USPSTF recommendations do not apply to women at high risk of breast cancer due to family history or genetic factors; in these cases, women are encouraged to consult with their primary care physician.

**Conclusions**

In summary, the importance of offering breast cancer screening is well documented. However, many women do not obtain this screening, which can result in delayed diagnosis and advanced breast cancer. In this review, we have emphasized the importance of increasing breast cancer screening across all populations, while acknowledging the challenges in achieving this goal.
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.
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-Barre syndrome, nerve 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), sarcoidosis, 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.

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Produced in USA.
Brief Summary of Prescribing Information
JEMPERLI (dostemilab-glyc) injection, for intravenous use

The following is a brief summary only; see full prescribing information for complete product information available at www.JEMPERLICHP.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 tumor response rate and durability of response [see Clinical Studies (1.4) of full prescribing information]. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

5 CONTRAINDICATIONS
None.

5 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-Ligand 1 (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. While immune-mediated adverse reactions usually abate during treatment with PD-1/PD-L1–blocking antibodies, they can also manifest after discontinuation of PD-1/PD-L1–blocking antibodies. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1–blocking antibodies. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions, such as fatigue, fever, diarrhea, dermatitis, and rash, and perform thorough investigations of patients experiencing symptoms. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

5.3 Complications of Allogeneic HSCT
JEMPERLI was permanently discontinued due to immune-mediated adverse reactions in 0.2% (2/515) of patients receiving JEMPERLI; both were Grade 3 (0.2%) adverse reactions. Colitis led to discontinuation of JEMPERLI in 1 of the 2 patients experiencing neoplasms.

5.4 Other 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 these patients, 1 patient died while receiving JEMPERLI. 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.

5.5 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 who 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-Barre syndrome, nerve paresis, autoimmune neuropathy.
- Cardio/Vascular: Myocarditis, periarteritis, vasculitis.
- Gastrointestinal: Pancreatitis, including increased 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/Immunologic): Autoimmune hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenia, solid organ transplant rejection.

5.6 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 4) occurred in 0.2% (1/515) of patients receiving JEMPERLI. All patients recovered from the infusion-related reactions.

Monitoring patients for signs and symptoms of infusion-related reactions, including hypotension, fever, hyperventilation, and tachycardia is necessary. Initiate management of infusion-related reactions as outlined in the full prescribing information.

5.7 Complications of Allotransplantation
Fetal and other serious complications can occur in patients who receive autologous hematopoietic stem cell transplantation (HCT), bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSC) before or after being treated with a PD-1/PD-L1–blocking antibody. Transplantation-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD,

Table 4. Adverse Reactions (≥10%) in Patients Receiving JEMPERLI

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Patients Receiving JEMPERLI</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>515</td>
<td>16.6%</td>
</tr>
<tr>
<td>Anemia</td>
<td>515</td>
<td>16.6%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>515</td>
<td>11.7%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>515</td>
<td>11.7%</td>
</tr>
<tr>
<td>Atrioventricular blockage</td>
<td>515</td>
<td>11.7%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>515</td>
<td>16.6%</td>
</tr>
<tr>
<td>Anemia</td>
<td>515</td>
<td>16.6%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>515</td>
<td>11.7%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>515</td>
<td>11.7%</td>
</tr>
<tr>
<td>Atrioventricular blockage</td>
<td>515</td>
<td>11.7%</td>
</tr>
</tbody>
</table>

*Note: This is a partial listing. For a complete list, see full prescribing information.*
5.3 Complications of Allogeneic HSCT (cont)
chronic GVHD; hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring 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 trial durations 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 14.1 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. Patients with anemia that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. 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 an adverse reaction occurred in ≥1% of patients who received JEMPERLI. Adverse reactions that required dosage interruption occurred in ≥1% of patients who received JEMPERLI. Adverse reactions that required dosage interruption occurred in ≥1% of patients who received JEMPERLI and were resolved in both patients. Systemic steroids to reduce the risk of permanent injury. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased leukocytes, decreased sodium, increased alkaline phosphatase, and increased aspartate aminotransferase.

The following is a brief summary only; see full Summary of Prescribing Information.

The safety of JEMPERLI was investigated in 267 patients with recurrent or advanced dMMR solid tumors enrolled in GARNET (see Clinical Studies 14.2 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. Patients with anemia that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. The median duration of exposure to JEMPERLI was 25 weeks (range: 1 to 139 weeks).

Serious adverse reactions occurred in 34% of patients receiving JEMPERLI. Serious adverse reactions (≥2% of patients) included: abdominal pain (3.7%), sepsis (2.6%), and acute kidney injury (2.2%). Fatal adverse reaction occurred in 1 patient who received JEMPERLI due to respiratory failure. JEMPERLI was permanently discontinued due to adverse reactions in 5% of patients; the most common adverse reaction (≥1%) leading to discontinuation was increased alkaline aminotransferase (1.1%).

Dosage interruptions due to an adverse reaction occurred in 23% of patients who received JEMPERLI. Adverse reactions that required dosage interruption occurred in ≥1% of patients who received JEMPERLI were anemia, pneumonitis, diarrhea, adrenal insufficiency, increased alanine aminotransferase, and increased aspartate aminotransferase.

The most common adverse reactions (≥2%) were fatigue/asthenia, anemia, diarrhea, and nausea. The most common Grade 3 or 4 adverse reactions (≥2%) were anemia, fatigue/asthenia, increased transaminases, sepsis, and acute kidney injury. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased sodium, increased alkaline phosphatase, and decreased albumin.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>JEMPERLI N = 104</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
</tr>
<tr>
<td>Fatigue</td>
<td>48</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26</td>
</tr>
<tr>
<td>Constipation</td>
<td>20</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
</tr>
<tr>
<td>Blood and lymphatic system</td>
<td>23</td>
</tr>
<tr>
<td>Anemia</td>
<td>24</td>
</tr>
</tbody>
</table>

Metabolism and nutrition

- Decreased appetite: 14%
- Respiratory, thoracic, and mediastinal:
  - Cough: 14%

Skin and subcutaneous tissue

- Pruritus: 14%

Infections

- Urinary tract infection: 13%

Musculoskeletal and connective tissue

- Myalgia: 12%

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

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>
<thead>
<tr>
<th>Laboratory Test</th>
<th>JEMPERLI N = 104</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>37</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>21</td>
</tr>
<tr>
<td>Chemistty</td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>30</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></td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>26</td>
</tr>
<tr>
<td>Increased calcium</td>
<td>15</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>15</td>
</tr>
</tbody>
</table>

- Consists of new onset of laboratory abnormality or worsening of baseline laboratory abnormality.

Mismatch Repair Deficient or Recurrent 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 14.2 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. Patients with anemia that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. The median duration of exposure to JEMPERLI was 25 weeks (range: 1 to 139 weeks).

Serious adverse reactions occurred in 34% of patients receiving JEMPERLI. Serious adverse reactions (≥2% of patients) included: abdominal pain (3.7%), sepsis (2.6%), and acute kidney injury (2.2%). Fatal adverse reaction occurred in 1 patient who received JEMPERLI due to respiratory failure. JEMPERLI was permanently discontinued due to adverse reactions in 5% of patients; the most common adverse reaction (≥1%) leading to discontinuation was increased alkaline aminotransferase (1.1%).

Dosage interruptions due to an adverse reaction occurred in 23% of patients who received JEMPERLI. Adverse reactions that required dosage interruption occurred in ≥1% of patients who received JEMPERLI were anemia, pneumonitis, diarrhea, adrenal insufficiency, increased alanine aminotransferase, and increased aspartate aminotransferase.

The most common adverse reactions (≥2%) were fatigue/asthenia, anemia, diarrhea, and nausea. The most common Grade 3 or 4 adverse reactions (≥2%) were anemia, fatigue/asthenia, increased transaminases, sepsis, and acute kidney injury. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased sodium, increased alkaline phosphatase, and decreased albumin.

Table 4 summarizes the adverse reactions that occurred in ≥10% of patients with dMMR recurrent or advanced solid tumors in GARNET.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>JEMPERLI N = 267</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
</tr>
<tr>
<td>General and administration site</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>42</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>12</td>
</tr>
<tr>
<td>Blood and lymphatic system</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>30</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
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<tr>
<td>Nausea</td>
<td>22</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>15</td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
</tr>
</tbody>
</table>

Metabolism and nutrition

- Decreased appetite: 14%
- Respiratory, thoracic, and mediastinal:
  - Cough: 14%

Infections

- Urinary tract infection: 13%

Musculoskeletal and connective tissue

- Myalgia: 12%

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

- Includes increased alanine aminotransferase, increased aspartate aminotransferase, and increased transaminases, and hypertransaminasemia.
6.1 Clinical Trials Experience (cont)

Clinically relevant adverse reactions in <10% of patients who received JEMPERLI included:
- Endocrine Disorders: Hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, autoimmune thyroiditis.
- Eye Disorders: Uveitis.
- Gastrointestinal Disorders: Colitis, enterocolitis, enterocolitis hemorrhage, pancreatitis, acute pancreatitis.
- General Disorders and Administration Site Conditions: Chills, Injury, Poisoning, and Procedural Complications: Infusion related reaction.
- Hematopoietic Disorders: Hematocytopenia injury.
- Musculoskeletal and Connective Tissue Disorders: Myalgia.
- Respiratory, Thoracic, and Mediastinal Disorders: Pneumonitis, interstitial lung disease.

Table 5 summarizes laboratory abnormalities worsening from baseline to Grade 3 or 4 in ≥1% of patients with dMMR recurrent or advanced solid tumors in GARNET.

### Table 5. Laboratory Abnormalities that Worsened from Baseline to Grade 3 or 4 Occurring in ≥1% of Patients with dMMR Recurrent or Advanced Solid Tumors in GARNET

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>JEMPERLI N = 267</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades†</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>33</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>18</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>12</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>26</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>26</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>26</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>22</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>21</td>
</tr>
<tr>
<td>Increased total bilirubin</td>
<td>7</td>
</tr>
<tr>
<td><strong>Electrolytes</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>21</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>16</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>14</td>
</tr>
<tr>
<td>Increased potassium</td>
<td>14</td>
</tr>
<tr>
<td>Increased calcium</td>
<td>1</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>4.1</td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*Concentrations of new onset of laboratory abnormality or worsening of baseline laboratory abnormality.

6.2 Immunogenicity

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

The immunogenicity of dostarlimab was evaluated in GARNET. Treatment-emergent antidualing antibodies (ADAs) against dostarlimab-gxly were detected in 2.1% of 384 patients who received dostarlimab-gxly at the recommended dosage. Neutralizing antibodies were detected in 1% of patients. Because of the small number of patients who developed ADAs, the effect of immunogenicity on the efficacy and safety of dostarlimab-gxly is inconclusive.

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)] of 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 immunemediated rejection of the developing fetus resulting in fetal death [see Data]. Human IgG3 immunoglobulins (IgG3) 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.

In the U.S. general population, the estimated background rate of major birth defects is 2% to 4% and 15% to 20%, respectively. Data for Animal Data: Animal reproduction studies have not been conducted with JEMPERLI to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering JEMPERLI during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/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 immunemediated disorders or altering the normal immune response.

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**

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).

**Immunemediated Adverse Reactions**

Inform patients of the potential for immunemediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid or other treatment and interruption or discontinuation of JEMPERLI. These reactions may include:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for new 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 (5.1)].
- Immune-mediated endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, thyroiditis, adrenal insufficiency, hypophysitis, or type 1 diabetes mellitus [see Warnings and Precautions (5.1)].
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis [see Warnings and Precautions (5.1)].
- Severe skin reactions: Advise patients to contact their healthcare provider immediately for any signs or symptoms of severe skin reactions, SJS, TEN, or DRESS [see Warnings and Precautions (5.1)].
- Other immunemediated adverse reactions:
  - Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new signs or symptoms [see Warnings and Precautions (5.1)].
  - Advise patients of the risk of solid organ transplant rejection and to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection [see Warnings and Precautions (5.1)].

**Infusion-Related Reactions**

- Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions [see Warnings and Precautions (5.2)].

**Complications of Allogeneic HSCT**

- Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications [see Warnings and Precautions (5.3)].

**Embryo-Fetal Toxicity**

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]
- Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after the last dose [see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)].

**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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Complaints About Prior Authorization Hit Boiling Point

THIS ISSUE OF Evidence-Based Oncology™ marks a pandemic milestone: all 3 medical conferences featured in this issue had in-person attendance for the first time in 2 years. One could feel the energy as colleagues shared a meal or caught up on personal news after a long break. We are thrilled to be back on the road as well—after 2 years off, the Institute for Value-Based Medicine® will relaunch with meetings in Nashville, Tennessee, and Tampa, Florida.

This excitement, however, was muted by tales of prior authorization nightmares, which have reached a boiling point. Meetings of the Association of Community Cancer Centers (ACCC) and the Community Oncology Alliance (COA) had panels on the topic, featuring some of the best-known leaders in provider-payer relations. Delays and denials of care are so burdensome that Barbara McAneny, MD, the New Mexico oncologist who is former president of the American Medical Association (AMA), reported that the AMA has hired a law firm and will sue if things do not improve.

These oncologists say “utilization management” (UM) has eclipsed the red tape of old and entered a new phase, which they attribute to recent mergers of payers and pharmacy benefit managers (PBMs). Until recently, UM meant jumping through hoops to get a patient on a new, unfamiliar therapy. It was not pleasant, but it was expected. Today, access to tried-and-true regimens can be hard to come by. McAneny reports that patients are being told to use outdated iron replacement drugs known to cause reactions. Texas Oncology’s Debra Patt, MD, PhD, MBA, said patients who are prescribed CDK4/6 inhibitors for breast cancer can end up on a schedule of 3 months on, 1 month off due to payer reauthorization delays.

Equally troubling is the inability of payers to keep pace with innovation in precision medicine. More than 1 oncology practice has hired a special staffer with expertise in gaining approvals for genomic testing, now considered a must when treating most types of breast or lung cancer. Without testing, patients cannot access the bumper crop of targeted therapies and immunotherapy cocktails that promise more years of life and, in some cases, fewer adverse effects than chemotherapy.

For payers, we ask, what is the end game? The costs for UM are high on both sides, and as experts at COA noted, a single trip to the emergency department can wipe the savings achieved when patients take old, toxic drugs. CMS could show leadership on this issue in Medicare and Medicaid, but instead these plans can be among the worst offenders. As one ACCC panelist put it, “prior authorization, in some cases, becomes almost a contract negotiation on a patient-by-patient basis.”

Prior authorization was meant to find the outliers in the health system, not force daily battles for basic care. As the pandemic eases, things could get worse as more patients are screened and receive diagnoses of later-stage cancers. Instead, it is time for health coverage to bring access. •

Sincerely,

Mike Hennessy Jr
President & CEO
INSIDE THIS ISSUE

SP122

Kashyap Patel, MD, president of the Community Oncology Alliance and CEO of Carolina Blood and Cancer Care Associates, welcomes attendees to the 2022 Community Oncology Conference, held March 16-18 in Kissimmee, Florida.

SP119-SP122

COMMENDARY

Redefining Cancer Care: Putting Equity, Quality, and Patients at the Center
SACHIN SENGUPTA

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COMMUNITY ONCOLOGY ALLIANCE 2022 COMMUNITY ONCOLOGY CONFERENCE
From Getting Paid to Managing Burnout, Panel Examines Future of Community Oncology Care
Pilot Projects to Reduce Cancer Care Disparities Deserve Support, Speakers Say
In Letter, COA Urges CMS to Do More to Rein in PBM Fees

REGULATORY & RESEARCH NEWS

COVERAGE BY MARY CAFFREY, MATTHEW GAVIDIA, REGULATORY & RESEARCH NEWS
SACHIN SENGUPTA

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Study on Types of Pain in MM Reveals Communication Inadequacies Between Physicians, Patients Possibility of Breast Cancer Overdiagnosis Should Inform Mammography Decisions
Study Evaluates Impact of AE Severity on Health State Utility for CART Treatment in LBCL

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Tumor Mutational Burden May Help Predict Immunotherapy Response in Metastatic NSCLC
Natural Killer Cell–Based Immunotherapy: A Less Toxic Treatment for Leukemia?

OLAPARIB APPROVALS EXPAND BREAST CANCER TREATMENT OPTIONS
FDA Approves Third Filgrastim Biosimilar: Releuko
FDA Approves Cita-cel to Treat R/R Multiple Myeloma
FDA Grants Breakthrough Device Designation to Foundation Medicine’s ctDNA Tracker
FDA Accepts sNDA for Zanubrutinib to Treat CLL/SLL

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We Need a Cancer Patient Bill of Rights

THE HARDEST JOURNEYS in this world begin with the words, “You have cancer.” As a physician who has uttered these words too many times to patients and families, I have a full realization of their weight. For many patients across this country, this transformational moment is one of profound disempowerment, often shrouded in fear and deep uncertainty. As clinicians we must bring both compassion and a deep-seated humility when guiding a patient through a time in which everything that they and their family knew before has irreversibly changed. Their hopes, dreams, expectations, ambitions, and milestones are now predicated upon vanquishing a foe that is far too often shrouded in mystery, mythology, and implacability.

As patients and families begin their respective cancer journeys, often they must combat both cancer and a health care system that can be different or hostile to their needs. At these times, the readily deployable tools of health care efficiency—narrow networks, step therapy, prior authorizations, utilization management, appeals processes—all present an existential threat to their well-being and make an already arduous journey even more painful and dehumanizing. Truth be told, when the cost-centered, relentless quest to improve value in health care turns into an obsessive and relentless pursuit of the lowest cost care, the patient’s journey becomes all the more difficult. Physicians should never be forced to become gatekeepers instead of caregivers. The quest for a cure should not be a journey measured in the number of appeals and denials that it takes to get there.

The dynamic nature of a cancer journey is unlike any in health care. Although data from the American Cancer Society show survival rates improved by 31% between 1990 and 2018, too many patients still lack a path toward a cure. The profound value of access to innovative therapeutics and the dynamic evolution of genomics-informed treatments portend a future of continued dramatic improvements in care outcomes. Yet disparities in care access and outcomes abound. As the 2020 American Association for Cancer Research Progress Report made so clear, these disparities persist across racial, ethnic, economic, and geographic lines. For patients who are Medicaid beneficiaries, care outcomes continue to lag those of patients with commercial insurance. For the most vulnerable members of our society, the journey to wholeness is more difficult, more fraught, and more unpredictable.

It is time to ensure that the needs of patients with cancer and their families become the central guiding principle of value-based care. Late in 2021, the California State Assembly became the first in the US to pass a Cancer Patient Bill of Rights (See SPXXX). In a time of political polarization and hyperpartisanship, the resolution was passed by both houses of the assembly in a unanimous vote. Cancer recognizes no party affiliation, and the enormous human toll of this set of diseases has touched virtually everyone in the country with an indiscriminate brutality. As such, we are inescapably united in our desire to defeat cancer.

The Cancer Patient Bill of Rights aims to ensure that all patients understand their diagnoses, have access to the latest care insights and precision medicine solutions, have access to necessary subspecialty care, have scalable access to whatever site of care can best address their needs during that part of their treatment journey, and can enroll in potentially lifesaving clinical trials without delay or undue barriers to access.

Over the past year in Evidence-Based Oncology™, we have reviewed the dynamically evolving nature of cancer care, spoken with experts on care disparities, and listened to health care transformation leaders point toward sustainable solutions for better systems of care. Each journey begins with a first step. The Cancer Patient Bill of Rights is one of those first steps. As we move toward the realization of more equitable care, care without barriers or unnecessary delays, and better outcomes for more patients, we look toward the community of cancer leaders and stakeholders, including community and academic physicians, systems leaders, diagnostic and therapeutic innovation creators, and policy makers to make this goal a reality.

Joseph Alvarnas, MD

EDITORIAL MISSION

To present policy makers, payers, and providers with the clinical, pharmacoeconomic, and regulatory information they need to improve efficiency and outcomes in cancer care.

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WHEN NAVIGATING THE DIFFICULTIES OF MULTIPLE MYELOMA IN THE REAL WORLD, YOU NEED
DURABLE STRENGTH

THE NINLARO® (Ixazomib) REGIMEN* OFFERS EXTENDED EFFICACY AND MANAGEABLE TOLERABILITY1-6

The NINLARO regimen extended median PFS by ~6 months vs the Rd regimen.* Median PFS: 20.6 vs 14.7 months for the NINLARO and Rd regimens, respectively; HR=0.74 (95% CI, 0.59-0.94); P=0.012.1,4

Continuous treatment with a proteasome inhibitor (PI)-based regimen is associated with clinical benefits in multiple myeloma.1,7,8

*The NINLARO regimen included NINLARO+lenalidomide+dexamethasone. The Rd regimen included placebo+lenalidomide+dexamethasone.

TOURMALINE-MM1: a global, phase 3, randomized (1:1), double-blind, placebo-controlled study that evaluated the safety and efficacy of NINLARO (an oral PI) vs placebo, both in combination with lenalidomide and dexamethasone, until disease progression or unacceptable toxicity in 722 patients with relapsed and/or refractory multiple myeloma who received 1-3 prior therapies.

NINLARO is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

• **Thrombocytopenia** has been reported with NINLARO. During treatment, monitor platelet counts at least monthly, and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines. Adjust dosing as needed. Platelet nadirs typically occurred between Days 14-21 of each 28-day cycle and recovered to baseline by the start of the next cycle.

• **Gastrointestinal Toxicities**, including diarrhea, constipation, nausea and vomiting, were reported with NINLARO and may occasionally require the use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea resulted in the discontinuation of one or more of the three drugs in 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for severe symptoms.

Please see additional Important Safety Information on the next page and accompanying Brief Summary.
• **Peripheral Neuropathy** (predominantly sensory) was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens. Monitor patients for symptoms of peripheral neuropathy and adjust dosing as needed.

• **Peripheral Edema** was reported with NINLARO. Monitor for fluid retention. Investigate for underlying causes when appropriate and provide supportive care as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.

• **Cutaneous Reactions**: Rash, most commonly maculo-papular and macular rash, was reported with NINLARO. Rash resulted in discontinuation of one or more of the three drugs in < 1% of patients in both regimens. Manage rash with supportive care or with dose modification.

• **Thrombotic Microangiopathy**: Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received NINLARO. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop NINLARO and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting NINLARO. The safety of reinitiating NINLARO therapy in patients previously experiencing TTP/HUS is not known.

• **Hepatotoxicity** has been reported with NINLARO. Drug-induced liver injury, hepatocellular injury, hepatic steatois, hepatitis cholestatic and hepatotoxicity have each been reported in < 1% of patients treated with NINLARO. Events of liver impairment have been reported (6% in the NINLARO regimen and 5% in the placebo regimen). Monitor hepatic enzymes regularly during treatment and adjust dosing as needed.

• **Embryo-fetal Toxicity**: Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the final dose. NINLARO can cause fetal harm.

**ADVERSE REACTIONS**

The most common adverse reactions (≥ 20%) in the NINLARO regimen and greater than the placebo regimen, respectively, were diarrhea (42%, 36%), constipation (34%, 25%), thrombocytopenia (78%, 54%; pooled from adverse events and laboratory data), peripheral neuropathy (28%, 21%), nausea (26%, 21%), peripheral edema (25%, 18%), vomiting (22%, 11%), and back pain (21%, 16%). Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhea (2%).

**DRUG INTERACTIONS**: Avoid concomitant administration of NINLARO with strong CYP3A inducers.

**SPECIAL POPULATIONS**

- **Hepatic Impairment**: Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment.
- **Renal Impairment**: Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis. NINLARO is not dialyzable.
- **Lactation**: Advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.

**REFERENCES**:


Please see accompanying Brief Summary on the following pages.
5.6 Thrombotic Microangiopathy: Thrombocytopenia has been reported with NINLARO with thrombotic microangiopathy between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. Three percent of patients in the NINLARO regimen and 1% of patients in the placebo regimen had a platelet count ≤ 10,000/mm³ during treatment. Less than 1% of patients in both regimens had a platelet count ≤ 5000/mm³ during treatment. Discontinuations due to thrombocytopenia were similar in both regimens (< 1% of patients in the NINLARO regimen and 2% of patients in the placebo regimen discontinued one or more of the three drugs).The rate of platelet transfusions was 6% in the NINLARO regimen and 5% in the placebo regimen. Consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.

5.7 Peripheral Neuropathy: The majority of peripheral neuropathy adverse reactions were Grade 1 (18% in the NINLARO regimen and 14% in the placebo regimen) and Grade 2 (8% in the NINLARO regimen and 5% in the placebo regimen). The majority of peripheral neuropathy adverse reactions were Grade 1 (< 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen). Adjust dosing for Grade 3 or 4 symptoms.

5.8 Embryo-Fetal Toxicity: NINLARO can cause fetal harm when administered to a pregnant woman based on the mechanism of action and findings in animal studies. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the final dose.

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 safety population from the randomized, double-blind, placebo-controlled clinical study included 720 patients with relapsed and/or refractory multiple myeloma, who received NINLARO in combination with lenalidomide and dexamethasone (NINLARO regimen; N = 360) or placebo in combination with lenalidomide and dexamethasone (placebo regimen; N = 360).

The most frequently reported adverse reactions (≥ 20%) in the NINLARO regimen and greater than the placebo regimen were diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain. Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhea (2%). For each adverse reaction, one or more of the three drugs was discontinued in ≤ 1% of patients in the NINLARO regimen.

Patients with a ≥ 5% Difference Between the NINLARO Regimen and the Placebo Regimen

Table 4: Non-Hematologic Adverse Reactions Occurring in ≥ 5% of Patients with a ≥ 5% Difference Between the NINLARO Regimen and the Placebo Regimen (All Grades, Grade 3 and Grade 4)

<table>
<thead>
<tr>
<th>NINLARO + Lenalidomide and Dexamethasone N=360</th>
<th>Placebo + Lenalidomide and Dexamethasone N=360</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>System Organ Class / Preferred Term</strong></td>
<td><strong>All</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Grade 3</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Grade 3</strong></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>69 (19)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>100 (28)</td>
</tr>
<tr>
<td>Peripheral neuropathy*</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>151 (42)</td>
</tr>
<tr>
<td>Constipation</td>
<td>122 (34)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>79 (22)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>68 (19)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>74 (21)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>91 (25)</td>
</tr>
</tbody>
</table>

Note: Adverse reactions included as preferred terms are based on MedDRA version 16.0.

*Represents a pooling of preferred terms

Table 5 represents pooled information from adverse event and laboratory data.

Table 8: Thrombocytopenia and Neutropenia

<table>
<thead>
<tr>
<th>NINLARO + Lenalidomide and Dexamethasone N=360</th>
<th>Placebo + Lenalidomide and Dexamethasone N=360</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any Grade</strong></td>
<td><strong>N (%)</strong></td>
</tr>
<tr>
<td><strong>Grade 3-4</strong></td>
<td><strong>Any Grade</strong></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>281 (78)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>240 (67)</td>
</tr>
</tbody>
</table>

*Represents a pooling of preferred terms

Herpes Zoster

Herpes zoster was reported in 4% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Antiviral prophylaxis was allowed at the healthcare provider’s discretion. Patients treated in the NINLARO regimen who
Brief Summary (cont’d)

received antiviral prophylaxis had a lower incidence (< 1%) of herpes zoster infection compared to patients who did not receive prophylaxis (6%).

Eye Disorders
Eye disorders were reported with many different preferred terms but in aggregate, the frequency was 26% in patients in the NINLARO regimen and 16% of patients in the placebo regimen. The most common adverse reactions were blurred vision (6% in the NINLARO regimen and 3% in the placebo regimen), dry eye (5% in the NINLARO regimen and 1% in the placebo regimen), and conjunctivitis (6% in the NINLARO regimen and 1% in the placebo regimen). Grade 3 adverse reactions were reported in 2% of patients in the NINLARO regimen and 1% in the placebo regimen.

Adverse Reactions Reported Outside of the Randomized Controlled Trial

The following serious adverse reactions have each been reported at a frequency of < 1%: acute febrile neutrophilic dermatosis (Sweet’s syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura.

7 DRUG INTERACTIONS

7.1 Strong CYP3A Inhibitors: Avoid concomitant administration of NINLARO with strong CYP3A inducers (such as rifampin, phenytoin, carbamazepine, and St. John's Wort).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Risk Summary: Based on its mechanism of action and data from animal reproduction studies, NINLARO can cause fetal harm when administered to a pregnant woman. There are no available data on NINLARO use in pregnant women to evaluate drug-associated risk. Ibazomib caused fetal toxicity in pregnant rabbits and rats at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. Advise pregnant women of the potential toxic effects to a fetus. In the U.S. general population, the background rate of major birth defects and miscarriage in commercially insured and medicare populations was 6% in the NINLARO regimen and 5% in the placebo regimen. There were no Grade 4 or 5 adverse reactions reported in both regimens included maculo-papular and macular rash. Rash was 6% in the NINLARO regimen and 5% in the placebo regimen. There were no Grade 4 or 5 adverse reactions reported in both regimens.

8.2 Lactation: Risk Summary: There are no data on the presence of ibazomib or its metabolites in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Because of the potential for serious adverse reactions from NINLARO in a breastfed infant, advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.

8.3 Females and Males of Reproductive Potential: NINLARO can cause fetal harm when administered to pregnant women. Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating NINLARO.

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

8.5 Geriatric Use: Of the total number of subjects in clinical studies of NINLARO, 55% were 65 and over, while 17% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment: NINLARO is not expected to have a clinically relevant impact on the clearance of ibazomib in patients with moderate or severe hepatic impairment, the mean AUC increased by 20% when compared to patients with normal hepatic function. Reduce the starting dose of NINLARO in patients with moderate or severe hepatic impairment.

8.7 Renal Impairment: In patients with severe renal impairment or ESRD requiring dialysis, the mean AUC increased by 39% when compared to patients with normal renal function. Reduce the starting dose of NINLARO in patients with severe renal impairment or ESRD requiring dialysis. NINLARO is not dialyzable and therefore can be administered without regard to the timing of dialysis.

10 OVERDOSAGE: Overdosage, including fatal overdosage, has been reported in patients taking NINLARO. Manifestations of overdosage include adverse reactions reported at the recommended dosage. Serious adverse reactions reported with overdosage include severe nausea, vomiting, diarrhea, aspiration pneumonia, multiple organ failure and death.

In the event of an overdosage, monitor for adverse reactions and provide appropriate supportive care. NINLARO is not dialyzable.

17 PATIENT COUNSELING INFORMATION

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

- Advise patients to take NINLARO exactly as prescribed.
- Advise patients to take NINLARO once a week on the same day at approximately the same time for the first three weeks of a four-week cycle. The importance of carefully following all dosage instructions should be discussed with patients starting treatment. Advise patients to take the recommended dosage as directed, because overdosage has led to deaths.
- Advise patients to take NINLARO at least one hour before or at least two hours after food.
- Advise patients that NINLARO and dexamethasone should not be taken at the same time, because dexamethasone should be taken with food and NINLARO should not be taken with food.
- Advise patients to swallow the capsule whole with water. The capsule should not be crushed, chewed or opened.
- Advise patients that direct contact with the capsule contents should be avoided. In case of capsule breakage, avoid direct contact of capsule contents with the skin or eyes. If contact occurs with the skin, wash thoroughly with soap and water. If contact occurs with the eyes, flush thoroughly with water.
- If a patient misses a dose, advise them to take the missed dose as long as the next scheduled dose is ≥ 72 hours away. Advise patients not to take a missed dose if it is within 72 hours of their next scheduled dose.
- If a patient vomits after taking a dose, advise them not to repeat the dose but resume dosing at the time of the next scheduled dose.
- Advise patients to store capsules in original packaging, and not to remove the capsule from the packaging until just prior to taking NINLARO.

Thrombocytopenia: Advise patients that they may experience low platelet counts (thrombocytopenia). Signs of thrombocytopenia may include bleeding and easy bruising. [see Warnings and Precautions (5.1)].

Gastrointestinal Toxicities: Advise patients they may experience diarrhea, constipation, nausea and vomiting and to contact their healthcare providers if these adverse reactions persist [see Warnings and Precautions (5.2)].

Peripheral Neuropathy: Advise patients to contact their healthcare providers if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the arms or legs [see Warnings and Precautions (5.3)].

Peripheral Edema: Advise patients to contact their healthcare providers if they experience unusual swelling of their extremities or weight gain due to swelling [see Warnings and Precautions (5.4)].

Cutaneous Reactions: Advise patients to contact their healthcare providers if they experience new or worsening rash [see Warnings and Precautions (5.5)].

Hypersensitivity, Microangiopathy: Advise patients to seek immediate medical attention if any signs or symptoms of thrombotic microangiopathy occur [see Warnings and Precautions (5.6)].

Hepatotoxicity: Advise patients to contact their healthcare providers if they experience jaundice or right upper quadrant abdominal pain [see Warnings and Precautions (5.7)].

Other Adverse Reactions: Advise patients to contact their healthcare providers if they experience signs and symptoms of acute febrile neutrophilic dermatosis (Sweet’s syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura [see Adverse Reactions (6.1)].

Embryo-Fetal Toxicity: Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)].

Advise females of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the final dose. Advise women using hormonal contraceptives to also use a barrier method of contraception [see Use in Specific Populations (8.1)].

Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the final dose.

Concomitant Medications: Advise patients to speak with their healthcare providers about any other medication they are currently taking and before starting any new medications.

Please see full Prescribing Information for NINLARO at NINLAROhcp.com.

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OneOncology’s Arrowsmith Looks Forward to Real-time Dynamics in Clinical Pathways

MARY CAFFREY

THE ROLE OF CLINICAL PATHWAYS is evolving, said Edward Arrowsmith, MD, MPH, who in January became medical director for Clinical Pathways across OneOncology, a Nashville, Tennessee-based network that allows its community oncology practices to collaborate on clinical, technological, and research initiatives at scale. Arrowsmith, a medical oncologist in Chattanooga, also serves as executive director of clinical informatics for Tennessee Oncology, one of the founding practices of the network.

As described by Hipp et al, clinical pathways allow practices “to reduce variations in practice and align decisions with evidence-based medicine, operational efficiency, and quality.”

Across OneOncology, Arrowsmith said, pathways offer a vehicle for physicians to agree on best practices and to implement them throughout the network’s 13 member practices. The process, he said, is led by Lisa Sowinski-Raff, PharmD, BCPS, BCPP, who is senior director of pharmacy, therapeutics, and pathways at OneOncology.

Arrowsmith spoke with Evidence-Based Oncology™ (EBO) about his role and the future of clinical pathways in a recent interview. This interview has been edited for length and clarity.

EBO: Can you describe your role as the medical director for clinical pathways, and how you work with practices across OneOncology?

ARROWSMITH: This is still very much a work in progress in that we have a long way to go to fully enact our vision—we the pathways team having a team-based approach—led by Lisa Raff—to do 2 big things. One is to coordinate the expert opinion of the physicians; all the OneOncology practices get a set of clinical best practices. And the second is to help practices implement them.

I think that’s what sets us apart from other pathways programs; in some cases, you create a PDF or maybe an electronic tool and that’s the end of the process. We do other things in...analytically and in identifying patients, particularly for targeted therapeutics. For example, how do we integrate next-generation sequencing to make sure we’re finding every patient with a KRAS [G12C] mutation? There are many therapies [that] are typical for what we’ve been doing for a long time—including targeted therapy, cytotoxic chemotherapy, immunotherapy. But there are more new treatments coming on board that are different—either in their testing or their [adverse] effects, or in how they’re given [to patients]. For example, the recent approval (of tenofovafib-trb) for uveal melanoma involves HLA (human leukocyte antigen) testing. Or, what can we expect with an upcoming approval of a radiopharmaceutical for prostate cancer? These are examples of where helping practices know how to do testing and administer those drugs is helpful. Sharing clinical and operational expertise across the network is an important part of what we do.

We’re tightly connected with provider education. When something comes on board or there’s a change in a pathway, we’ll have a video and handouts or even live programs to make sure everyone knows which patients should receive the therapy and how to best give that therapy. We also work with a product called Flatiron Assist™; Flatiron (Health), the maker of OncoEMR [electronic medical record], is our technology partner. Flatiron has a point-of-care tool for use when you’re ordering a regimen and we are working with [Flatiron] to customize it, so that when physicians are ordering it’s easy to follow the pathways for their patients.

EBO: Pathways have been around for a while now. What kind of feedback, good and bad, do you receive from the physicians in practice? Do physicians like using pathways, or are there still things that need work?

ARROWSMITH: The practices in OneOncology are focused on optimizing patient care. Philosophically, we’re all aligned around having a pathways program—and particularly one like this, where we have a voice in it, rather than, say, an insurer’s pathway program, where we wouldn’t have a voice. It’s really around implementing the pathways where we get a lot of feedback—both around the kind of tools and education, such as Flatiron Assist. But this is an ongoing effort to help busy clinicians follow the pathways. Everyone is trying to do what’s best for their patient. I always use the example of a physician who’s alone in office, maybe in a rural setting; this doctor sees lots of patients and every type of cancer that comes through the door, because we’re trying to treat patients in their own communities. On a busy afternoon, when [that physician] is behind schedule and has a sick patient with a lot of needs, how can we help that physician do his or her best to follow what is a changing pathway in that setting? It’s that implementation piece where we get a lot of feedback.

EBO: You coauthored an article about a case study in non–small cell lung cancer that addressed the issue of balancing clinical pathways with specific conditions as we move forward in precision medicine. How does that case illustrate the balancing issues that come up today?

ARROWSMITH: That’s a piece we wrote because we were in a variety of contexts—sometimes arguing with insurers, sometimes with others—about what we saw as a change in the role of pathways based on changes in oncology. A little history is helpful: in my view, pathways started with a paper that [Dr] Joan Schiller wrote for ECOG [Eastern Cooperative Oncology Group] in the New England Journal of Medicine, comparing 4 different platinum doublets for non–small cell lung cancer that showed that each of those 4 therapies was equivalent. That led to a critical paper in the pathways movement, where The US Oncology Network showed that by choosing generics for situations like that, mainly generic paclitaxel, instead of name brands, such as Gemzar (for gemcitabine) or Taxotere (for docetaxel), that you could reduce costs.

What we were arguing in our paper is that era had passed. For the majority of patients with non–small cell lung cancer, there really was one best therapy. If they have an EGFR mutation, there’s one appropriate therapy; if they have a ROS1 or an ALK mutation, there is an appropriate therapy; Those 4 platinum doublets for adenocarcinoma or nonsquamous carcinomas had been replaced with name-brand pemetrexed (Pemfexy), and immunotherapy had entered the market. We were really arguing that in that era, there really was one therapy, and to think of pathways as a great tool for reducing costs was probably not the right way to think about pathways—the pathways were more a way to demonstrate high-quality clinical care. Since we wrote that paper, I think there has been a bit of a shift in the oncology landscape. One huge thing is the development of biosimilars that have come on the market. And so that’s an opportunity, with standardization in a practice, for a biosimilar to allow continuation of excellent quality care but the possibility
of creating more value by reducing costs. There are more examples where there might be 2 treatments that look very similar...competing immunotherapies, or in some settings such as BRAF-mutant mela
mona, where there are some targeted therapies that appear to have the same mechanism of action and very similar outcomes. That era of clinical equipoise may be returning for certain disease states.

EBO: How do you see the use of pathways evolving both within a practice and across the network with OneOncology?

ARROWSMITH: There are a few things. One is that over the [past] 12 to 18 months, we’re really seeing an explosion in the rate of change in clinical care. In some weeks, there are 2 or 3 FDA approvals in oncology. For us, it’s critical that we not wait for the pathways committee to meet quarterly for updates on new data, but to update pathways in real time to help patients. One big change I see in the future is that we have data analytics to help you find the right patient, but you also do want to do analysis on the back end to see how you’re doing. Having that sort of 360-degree process is what we think is best for value-based care arrangements. Contracts in the future will consider this dynamic change in oncology, so that payers and OneOncology practices can work together to develop what’s really best for all the stakeholders in cancer care.

ARROWSMITH: We see pathways as a 360-degree process, where you have a pathway, you have data analytics to help you find the right patient, but you also do want to do analysis on the back end to see how you’re doing. Having that sort of 360-degree process is what we think is best for value-based care arrangements. Contracts in the future will consider this dynamic change in oncology, so that payers and OneOncology practices can work together to develop what’s really best for all the stakeholders in cancer care.

FDA ACTIONS

Axi-cel Approved in Second Line for LBCL, Expands CAR T Pool by 11,000 in US Alone

Mary Caffrey

THE FDA ON APRIL 1 authorized the use of Kite Pharma’s axicabtagene ciloleucel (axi-cel) for patients who have relapsed just once from large B-cell lymphoma (LBCL), a change that could expand the pool of patients eligible for chimeric antigen receptor (CAR) T-cell therapy by 11,000 just in the United States.1,2 This change will expand use of a high-cost cancer treatment from the sickest patients to those who are comparatively fit, raising new questions for payers and policy makers.

“This approval brings that hope to more patients by enabling the power of CAR T-cell therapy to be used earlier in the treatment journey,” Christi Shaw, CEO of Kite Pharma, said in a statement.1 This milestone has been years in the making. On behalf of the entire Kite community, we would like to thank the patients and physicians who have been on this journey with us.”

The expanded use of axi-cel, sold as Yescarta, while not unexpected, nonetheless represents uncharted territory in cancer care at a time when clinicians are highlighting problems with utilization management. However, Lori Ann Leslie, MD, director of indolent lymphoma and chronic lymphocytic leukemia research programs at John Theurer Cancer Center, said she looked forward to discussing the treatment with patients as early as the week of April 4.

“I’ve talked to a few of my patients about the pending approval, and how treatment landscapes are evolving,” Leslie said in an interview with Evidence-Based Oncology.2 “Once we see the label, we will see—it may be very relevant for them.”

The approval is based data from ZUMA-7, which showed that patients treated with axi-cel were 2.5 times more likely to be alive after 2 years without the need for additional treatment than those who received standard of care (40.5% vs 16.3%).2 During his presentation at the 2021 meeting of the American Society of Hematology (ASH), Moffitt Cancer Center’s Frederick Locke, MD, highlighted a key point: Of the patients randomized to axi-cel, 94% successfully received CAR T-cell treatment; in comparison, only 36% of those randomized to standard of care received high-dose therapy and autologous stem-cell therapy (ASCT). The question will be whether the payer infrastructure can manage a wave of new patients seeking treatment with axi-cel, including some who conceivably could be treated with the existing standard of care, which is high-dose therapy followed by ASCT. Payer delays in approving axi-cel could make this expensive treatment less effective once it reaches patients, and it could force clinicians to order rounds of chemotherapy to stabilize patients during the manufacturing process, adding to costs. For their part, Kite Pharma officials said they will use the same network of 112 authorized centers to administer the treatments that they’ve been using since axi-cel was first approved for third-line treatment in 2017. Kite officials say the process to secure payer approval for CAR T-cell therapy has greatly improved since that time.

Cost is a major consideration for payers. Axil-cell treatments have been listed at $373,000 and that does not include the cost of hospitalization or treatment of adverse events, which can include cytokine release syndrome (CRS). Over time, management of CRS has vastly improved.2

REFERENCES


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REFERENCES


Important Safety Information

Warnings and Precautions

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue at any time after starting treatment. While immune-mediated adverse reactions usually occur during treatment, they can also occur after discontinuation. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. Early identification and management are essential to ensuring safe use of PD-1/PD-L1–blocking antibodies. The definition of immune-mediated adverse reactions included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function 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 specialty consultation as appropriate.

Visit LIBTAYOhcp.com for more information.
Important Safety Information (cont’d)

Warnings and Precautions (cont’d)

Severe and Fatal Immune-Mediated Adverse Reactions (cont’d)

No dose reduction for LIBTAYO is recommended. In general, withhold LIBTAYO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue LIBTAYO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated adverse reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone equivalent per day within 12 weeks of initiating steroids.

Withhold or permanently discontinue LIBTAYO depending on severity. In general, if LIBTAYO requires interruption or discontinuation, administer systemic corticosteroid therapy (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 reactions are not controlled with corticosteroids.

Immune-mediated pneumonitis: LIBTAYO can cause immune-mediated pneumonitis. 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 3.2% (26/810) of patients receiving LIBTAYO, including Grade 4 (0.5%), Grade 3 (0.5%), and Grade 2 (2.1%). Pneumonitis led to permanent discontinuation in 1.4% of patients and withholding of LIBTAYO in 2.1% of patients. Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 58% of the 26 patients. Of the 17 patients in whom LIBTAYO was withheld, 9 reinitiated after symptom improvement; of these, 3/9 (33%) had recurrence of pneumonitis. Withhold LIBTAYO for Grade 2, and permanently discontinue for Grade 3 or 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated colitis: LIBTAYO can cause immune-mediated colitis. The primary component of immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1–blocking antibodies. In cases of corticosteroid-refractory immune-mediated colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 2.2% (18/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (1.1%). Colitis led to permanent discontinuation in 0.4% of patients and withholding of LIBTAYO in 1.5% of patients. Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 39% of the 18 patients. Of the 12 patients in whom LIBTAYO was withheld, 4 reinitiated LIBTAYO after symptom improvement; of these, 3/4 (75%) had recurrence. Withhold LIBTAYO for Grade 2 or 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated hepatitis: LIBTAYO can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 2% (16/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (1.4%), and Grade 2 (0.2%). Hepatitis led to permanent discontinuation of LIBTAYO in 1.2% of patients and withholding of LIBTAYO in 0.5% of patients. Systemic corticosteroids were required in all patients with hepatitis. Additional immunosuppression with mycophenolate was required in 19% (3/16) of these patients. Hepatitis resolved in 50% of the 16 patients. Of the 5 patients in whom LIBTAYO was withheld, 3 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence.

For hepatitis with no tumor involvement of the liver: Withhold LIBTAYO if AST or ALT increases to more than 3 and up to 8 times the upper limit of normal (ULN) or if total bilirubin increases to more than 1.5 and up to 3 times the ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 8 times the ULN or total bilirubin increases to more than 3 times the ULN.

For hepatitis with tumor involvement of the liver: Withhold LIBTAYO if baseline AST or ALT increases to more than 1 and up to 3 times ULN increases to more than 5 and up to 10 times ULN. Also, withhold LIBTAYO if baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 10 times ULN or if total bilirubin increases to more than 3 times ULN. If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue LIBTAYO based on recommendations for hepatitis with no liver involvement.

Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated endocrinopathies: For Grade 3 or 4 endocrinopathies, withhold until clinically stable or permanently discontinue depending on severity.

- Adrenal insufficiency: LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity. Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%). Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. LIBTAYO was not withheld in any patient due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these, 67% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff.

Please see additional Important Safety Information and Brief Summary of Prescribing Information on the following pages.
Important Safety Information (cont’d)

Warnings and Precautions (cont’d)

Severe and Fatal Immune-Mediated Adverse Reactions (cont’d)

Immune-mediated endocrinopathies: (cont’d)

- **Hypophysitis:** LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue depending on severity. Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient and withholding of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids were required in 67% (2/3) of patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cutoff.

- **Thyroid disorders:** LIBTAYO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity.

- **Thyroiditis:** Thyroiditis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) adverse reactions. No patient discontinued LIBTAYO due to thyroiditis. Thyroiditis led to withholding of LIBTAYO in 1 patient. Systemic corticosteroids were not required in any patient with thyroiditis. Thyroiditis had not resolved in any patient at the time of data cutoff. Blood thyroid stimulating hormone increased and blood thyroid stimulating hormone decreased have also been reported.

- **Hyperthyroidism:** Hyperthyroidism occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.9%). No patient discontinued treatment and LIBTAYO was withheld in 0.5% of patients due to hyperthyroidism. Systemic corticosteroids were required in 3.8% (1/26) of patients. Hyperthyroidism resolved in 50% of 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hyperthyroidism, 2 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hyperthyroidism.

- **Hypothyroidism:** Hypothyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%). Hypothyroidism led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. Hypothyroidism led to withholding of LIBTAYO in 1.1% of patients. Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 8.3% of the 60 patients. Majority of the patients with hypothyroidism required long-term thyroid hormone replacement. Of the 9 patients in whom LIBTAYO was withheld for hypothyroidism, 1 reinitiated LIBTAYO after symptom improvement; 1 required ongoing hormone replacement therapy.

- **Type 1 diabetes mellitus, which can present with diabetic ketoacidosis:** Monitor for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold LIBTAYO depending on severity. Type 1 diabetes mellitus occurred in 0.1% (1/810) of patients, including Grade 4 (0.1%). No patient discontinued treatment due to type 1 diabetes mellitus. Type 1 diabetes mellitus led to withholding of LIBTAYO in 0.1% of patients.

Immune-mediated nephritis with renal dysfunction: LIBTAYO can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%), and Grade 2 (0.4%). Nephritis led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients. Systemic corticosteroids were required in all patients with nephritis. Nephritis resolved in 80% of the 5 patients. Of the 3 patients in whom LIBTAYO was withheld, 2 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence. Withhold LIBTAYO for Grade 2 or 3 increased blood creatinine, and permanently discontinue for Grade 4 increased blood creatinine. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated dermatologic adverse reactions: LIBTAYO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1–blocking antibodies. Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%). Immune-mediated dermatologic adverse reactions led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients. Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reactions, 7 reinitiated LIBTAYO after symptom improvement; of these, 43% (3/7) had recurrence of the dermatologic adverse reaction. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold LIBTAYO for suspected SJS, TEN, or DRESS. Permanently discontinue LIBTAYO for confirmed SJS, TEN, or DRESS. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Other immune-mediated adverse reactions: The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 810 patients who received LIBTAYO 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.

- **Cardiac/vascular:** Myocarditis, pericarditis, and vasculitis. Permanently discontinue for Grades 2, 3, or 4 myocarditis.

- **Nervous system:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nure paressis, and autoimmune neuropathy. Withhold for Grade 2 neurological toxicities and permanently discontinue for Grades 3 or 4 neurological toxicities. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.
Important Safety Information (cont’d)

Warnings and Precautions (cont’d)

Severe and Fatal Immune-Mediated Adverse Reactions (cont’d)

Other immune-mediated adverse reactions: (cont’d)

- **Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss
- **Gastrointestinal:** Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis, stomatitis
- **Musculoskeletal and connective tissue:** Myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica
- **Endocrine:** Hypoparathyroidism
- **Other (hematologic/immune):** Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

Infusion-related reactions

Severe infusion-related reactions (Grade 3) occurred in 0.1% of patients receiving LIBTAYO as a single agent. Monitor patients for signs and symptoms of infusion-related reactions. The most common symptoms of infusion-related reaction were nausea, pyrexia, rash, and dyspnea. Interrupt or slow the rate of infusion for Grade 1 or 2, and permanently discontinue for Grade 3 or 4.

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, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring 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.

Embryo-fetal toxicity

LIBTAYO can cause fetal harm when administered to a pregnant woman due to an increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

Adverse Reactions

- In the pooled safety analysis of 810 patients, the most common adverse reactions (≥15%) with LIBTAYO were musculoskeletal pain, fatigue, rash, and diarrhea
- In the pooled safety analysis of 810 patients, the most common Grade 3-4 laboratory abnormalities (≥2%) with LIBTAYO were lymphopenia, hyponatremia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia

Use in Specific Populations

- **Lactation:** Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO
- **Females and males of reproductive potential:** Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO

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

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; PD-L1, programmed death ligand-1; ROS1, c-ros oncogene 1 receptor tyrosine kinase.


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Dosage and Administration (2.1) in the full prescribing information.

With adrenal insufficiency; of these 67% (2/3) remained on systemic corticosteroids. Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. LIBTAYO Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%) adverse reactions. Importantly, 1 patient discontinued LIBTAYO due to thyroid dysfunction, whereas 2 patients discontinued LIBTAYO due to hypophysitis. Thyroid disorders had been established in any patient at the time of data cutoff. Body thyroid stimulating hormone increased and blood thyroid stimulating hormone decreased had also been reported.

Hypothyroidism: Hypothyroidism occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.4%) adverse reactions. No patient discontinued treatment due to hypothyroidism. Hypothyroidism led to withholding of LIBTAYO in 0.5% of patients. Systemic corticosteroids were required in 3.8% (1/26) of patients with hypothyroidism. Hypothyroidism resolved in 50% of the 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hypothyroidism, 2 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hypothyroidism. Hypothyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (0.1%) adverse reactions in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.4%) adverse reactions. No patient discontinued treatment due to hypothyroidism. Hypothyroidism led to withholding of LIBTAYO in 0.1% of patients. Immune-Mediated Nephritis with Renal Dysfunction

LIBUTAYO can cause immune-mediated nephritis. The definition of immune-mediated nephritis included the requirement of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Immune-mediated nephritis occurred in 0.8% (8/810) patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Nephritis led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients. Systemic corticosteroids were reinitiated in 60% of the 8 patients. Of the 4 patients in whom LIBTAYO was withheld for nephritis, 2 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of nephritis.

Immune-Mediated Dermatologic Adverse Reactions

LIBUTAYO can cause immune-mediated rash or dermatitis. The definition of immune-mediated dermatologic adverse reaction included the requirement of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Immune-mediated rash occurred in 0.8% (8/810) patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Nephritis led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients. Systemic corticosteroids were reinitiated in 60% of the 8 patients. Of the 4 patients in whom LIBTAYO was withheld for nephritis, 2 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of nephritis.

Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of < 1% in 810 patients who received LIBTAYO or were reported with the use of other PD-1/PD-L1 blocking antibodies.

Cardiovascular: Myocarditis, pericarditis, vasculitis

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome / myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities. Some cases may be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis, stomatitis

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica

Endocrine: Hypothyroidism

Other hematologic/immune: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

Infusion-Related Reactions

Severe infusion-related reactions (Grade 3) occurred in 0.1% of patients receiving LIBTAYO as a single agent. Most of the patients had signs and symptoms of multi-organ involvement. The most common symptoms of infusion-related reaction were nausea, tyramina, rash and dyspnea. Intermittent or slow the rate of infusion or permanently discontinue LIBTAYO based on severity of reaction [see Dosage and Administration (2.3) in the full prescribing information].

Infections of Allogeneic HSC

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HCT) 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, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervention therapy between LIBTAYO and its blockade and allogeneic HSC. 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 HSC.
5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, LIBTAYO 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 rejections and the development of fetal toxicities resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose (see Use in Specific Populations (8.1, d, l)).

6 ADVERSE REACTIONS

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 described in Warnings and Precautions reflect exposure to LIBTAYO as a single agent in 810 patients in three open-label, single-arm, multicohort studies (Study 1423, Study 1540 and Study 1620), and one open-label randomized multi-center study (Study 1624). These studies included 219 patients with advanced CSCC (Studies 1425 and 1442), 132 patients with advanced BCC (Study 1432), 55 patients with NSCLC (Study 1624), and 194 patients with other advanced solid tumors (Study 1432). LIBTAYO was administered intravenously at doses of 3 mg/kg every 2 weeks (n=225), 300 mg every 3 weeks (n=543), or other doses (n=3; 1 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, 200 mg every 2 weeks). Among the 810 patients, 53% were exposed for ≥ 6 months and 25% were exposed for ≥ 12 months. In this pooled safety population, the most common adverse reactions (≥15%) were musculoskeletal pain, fatigue, rash, and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥2%) were lymphopenia, hypotension, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia.

Cutaneous Squamous Cell Carcinoma (CSCC)

The safety of LIBTAYO was evaluated in 219 patients with advanced CSCC (metastatic or locally advanced disease) in Study 1423 and Study 1540 (see Clinical Studies (14.1) in the full prescribing information). Of these 219 patients, 131 had mCSCC (nodal or distant) and 88 had aCSCC. Patients received LIBTAYO 1 mg/kg every 2 weeks (n=1), 3 mg/kg every 2 weeks (n=162) or 350 mg every 3 weeks (n=56) as an intravenous infusion. Grade 3 or 4 laboratory abnormalities (≥2%) were lymphopenia, hyponatremia, hypophosphatemia, increased aspartate aminotransferase, anemia and hyperkalemia.

Basal Cell Carcinoma (BCC)

The safety of LIBTAYO was evaluated in 132 patients with advanced BCC in a label-compliant, open-label, single-arm trial (Study 1620) (see Clinical Studies (14.2) in the full prescribing information). Patients received LIBTAYO 350 mg every 3 weeks as an intravenous infusion for up to 90 weeks or until disease progression or unacceptable toxicity. This median duration of exposure was 42 weeks (range: 2.4 to 94 weeks).

The safety population characteristics were: median age of 68 years (38 to 96 years), 83% male, 96% White, 53% ECOG performance score (PS) of 0 (44%) and 1 (56%).

Table 2 summarizes the adverse reactions that occurred in ≥10% of patients and Table 3 summarizes Grade 3 or 4 laboratory abnormalities worsening from baseline to Grade 3 or 4.

Table 2: Adverse Reactions in ≥10% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LIBTAYO N=219</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General and Administration Site</td>
<td>All Grades</td>
<td>%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Rash</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Arthritis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03</td>
<td>a. Composite term includes fatigue and asthenia</td>
<td>2</td>
</tr>
<tr>
<td>b. Composite term includes rash, maculopapular rash, pruritus and pruritus allergic</td>
<td>2</td>
<td>0.01</td>
</tr>
<tr>
<td>c. Composite term includes rash pruritic, dermatitis, erythema, urticaria</td>
<td>5</td>
<td>0.01</td>
</tr>
<tr>
<td>d. Composite term includes rash papular, erythema, urticaria</td>
<td>4</td>
<td>0.01</td>
</tr>
<tr>
<td>e. Composite term includes rash papular and pruritus</td>
<td>3</td>
<td>0.01</td>
</tr>
<tr>
<td>f. Composite term includes rash papular and pruritus allergic</td>
<td>2</td>
<td>0.01</td>
</tr>
<tr>
<td>g. Composite term includes rash papular and pruritus allergic</td>
<td>2</td>
<td>0.01</td>
</tr>
<tr>
<td>h. Composite term includes rash papular and pruritus allergic</td>
<td>2</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 3: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥ 1% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3-4(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>9</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>2</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>15</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>5</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>4</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>2</td>
</tr>
</tbody>
</table>

Toxicity graded per NCI CTCAE ≥ 4.03:
a. Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter

Table 4: Adverse Reactions in ≥10% of Patients with Advanced BCC Receiving LIBTAYO in Study 1620

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Grades</th>
<th>%</th>
<th>Grades 3-4</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>30</td>
<td>6.1</td>
<td>30</td>
<td>6.1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>33</td>
<td>5</td>
<td>33</td>
<td>5</td>
</tr>
<tr>
<td>Cutaneous disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>0</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
<td>0</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>22</td>
<td>0</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>15</td>
<td>0</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>2</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>14</td>
<td>2</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>0</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraines</td>
<td>12</td>
<td>1.5</td>
<td>12</td>
<td>1.5</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11</td>
<td>0</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>0</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03:
a. Composite term includes fatigue, asthenia, and malaise
b. Composite term includes rash, maculopapular rash, pruritus and pruritus allergic
b. Composite term includes rash papular and pruritus allergic
c. Composite term includes rash maculopapular, erythema, urticaria, dermatitis, papules, rash generalised, pruritus, rash erythematous, rash macular, rash papular, urticaria, pruritus and pruritus allergic
d. Composite term includes rash papular and pruritus allergic
e. Composite term includes rash papular and pruritus allergic
Table 6: Laboratory Abnormalities Worsening from Baseline in n = 1% of Patients with Advanced BCC Receiving LIBTAYO in Study 1629

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>2.2</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>3.1</td>
<td>1.5%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2.3</td>
<td>0.0%</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>2.3</td>
<td>0.0%</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>2.3</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Toxicity graded per NCI CTCAE v. 4.03

a. Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.

6.2 Immunogenicity

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

Anti-drug antibodies (ADA) were tested in 623 patients who received LIBTAYO. The incidence of cemiplimab-rwlc–treatment-emergent ADA was 2.2% using an electrochemiluminescent (ECL) bridging immunoassay; 0.4% were persistent ADA responses. In the patients who developed anti-cemiplimab-rwlc antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab-rwlc.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology (12.1) in the full prescribing information). There are no available data on the use of LIBTAYO 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 placenta; therefore, LIBTAYO has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with LIBTAYO to evaluate its effect on reproduction and fetal development. A central function of the PD-1-PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering LIBTAYO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations reported 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 cemiplimab-rwlc may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Females

Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

8.4 Pediatric Use

There are no available data on the use of LIBTAYO in patients younger than 18 years of age. Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

Of the 810 patients who received LIBTAYO in clinical studies, 32% were 65 years up to 75 years and 22% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 219 patients with mSCC or lSCC who received LIBTAYO in clinical studies, 34% were 65 years up to 75 years and 41% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 132 patients with BCC who received LIBTAYO in Study 1620, 27% were 65 years up to 75 years, and 32% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

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Evidence, Support, and Education Needed to Drive Precision Oncology, Accenture’s Bogdan Says

MARY CAFFREY

IMPROVING UPTAKE OF precision medicine in community oncology practices will require a multistep process to arm physicians with both the right data and the right support, along with a rethinking of how education occurs, according to a global leader in medical technology.

Boris Bogdan, MD, MBA, managing director and global lead, Medical Practice and Center of Excellence for Precision Oncology, Accenture, discussed a survey of oncologists’ views—along with recommendations on how to bolster precision medicine—during an interview with Evidence-Based Oncology.

The results and recommendations were included in Accenture’s 2021 report, “The Future Is Now: How to Drive Precision Oncology Adoption.” The report adds to the chorus calling for greater sharing of data and improved standardization, so that academic centers and community practices alike can continually improve data sets used worldwide. Accenture’s findings align with the discussion held with global experts in real-world evidence (RWE) during a symposium at the American Society of Hematology 63rd Annual Meeting & Exposition in December 2021.

Precision oncology is considered the future of cancer care; the Accenture report cites a 2019 study estimating that up to 50% of patients could benefit from this approach. And yet, Accenture’s engagement of 130 oncologists in the United States and Europe found that 29% reported the practice of matching a treatment to a particular patient was not widely adopted in their daily work.

Accenture has set out to hear directly from oncologists—especially those in community practice—about what it would take to achieve broader uptake of precision oncology, Bogdan said. This mission, he explained, “is to really understand what is it that they need in their everyday practice to be more successful.”

According to the report:

• 85% of respondents ranked outcomes and longitudinal data as the most critical data source to share.
• 20% or less of oncologists today do not routinely participate in molecular tumor boards or use clinical decision support tools.
• 66% of oncologists believe clinical practice is changing rapidly and will require them to master new skill sets.

“We’ve seen a significant difference between what somebody in a community practice needs vs somebody in academic medical center,” noted Bogdan, who is based on Basel, Switzerland. But both have needs in common: The groups of oncologists all have the desire to discuss specific therapies with colleagues.

The intersection between these two, he said, is the “sweet spot,” where the right type of data and decision support can make a difference. Technology can give community oncologists the same level of feedback and guidance that can be found within an academic center, where tumor boards allow for deep exchanges. Accenture’s report outlines a 3-step process:

1. Arming oncologists with the right evidence;
2. Offering clinical decision support to address uncertainties; and
3. Education that offers a “comprehensive foundational understanding of precision oncology.”

Giving oncologists at every level the right access to data, and the ability to discuss specific cases, is needed to take geography out of the equation in delivering quality care, Bogdan said. Already, some oncologists recommend genomic testing for every patient, although that is not the norm today.

And yet, Bogdan continued, even patients can gain access to testing, oncologists still have questions. What might be the right analytical diagnostic tools? What is the right biomarker?

Accenture’s engagement has shown the need for an educational component, with opportunities for peer-to-peer discussions on the best approach. The former practice of just picking up the phone and calling someone is insufficient, given the amount of information a community oncologist must absorb.

Moving from the era of “medicine by anecdote” to true evidence-based practice requires what Bogdan described as a middle step. If data sharing becomes uniform and widespread, the possibility exists for “medicine by crowdsourcing,” in that clinical opinion will still matter, but there will be strength in numbers and data behind it.

A community oncologist, Bogdan said, still appreciates the chance for a personal connection. “They appreciate having that quick break in the day to have chat and an exchange,” he said. This is especially true if access to a tumor board is limited or unavailable.

Developing support tools that can create these opportunities would be valuable, based on Accenture’s findings, he said. A key will be to bring standardization to the data sharing process, which Bogdan said will take effort given the lack of uniformity in Europe alone. Achieving data standardization will be a huge, expensive undertaking, Bogdan acknowledged, and the roles for academia, community oncology, payers, pharmaceutical companies, and the government are still being defined. But standardization and open source data sharing must happen.

“The quality of care 10 years from now shouldn’t be decided by whether you are living somewhere close to somebody who’s excellent,” Bogdan emphasized. “Rather, we must have a system in place, so that any place that you’re going to see an oncologist, they are enabled to make great decisions.

“We need to come to a point where we recognize that we cannot practice oncology in the future without the right data,” Bogdan said. “And when we talk about data, these are not hospital-specific data. These are data across systems—community and academic medical centers—all sharing to benefit the patient. That is where I hope we are going to get.”

REFERENCES


Association of 340B Contract Pharmacy Growth With County-Level Characteristics
Read more at: https://bit.ly/3NerJKd
Medical World News® is a first-of-its-kind 24-hour online program for health care professionals, by health care professionals. The site provides video editorial content on a variety of cutting-edge topics delivered through a livestream and on demand for all health care stakeholders, offering the latest news and information in an easily digestible, one-stop-shop format.

DEEP DIVE

Matthew Gavidia, associate editor for The American Journal of Managed Care® (AJMC®), interviews Michael Sun, a third-year medical student at the University of Chicago Pritzker School of Medicine, about a recent study in Health Affairs that analyzed the use of negative descriptors in the electronic health record (EHR). Using artificial intelligence, the investigators found that Black patients were more than 2.5 times as likely as White patients to have negative descriptors in the EHR. Sun notes that every team member who sees the patient will see these negative terms in the EHR, which can amount to “blaming the patient for their own medical needs.” The study was completed prior to “open notes” policies that give patients access to their EHR, and Sun says that patients could object to these terms if they see them in records. According to Sun, a drop in negative descriptors occurred during the COVID-19 pandemic, which could be attributed to the national spotlight on health care disparities. A key takeaway, he says, is that “health care providers can change their language.”

WELL-BEING CHECKUP

Kathy Oubre, MS, CEO of Pontchartrain Cancer Center, Covington, Louisiana, talks with associate editor Skylar Jeremias of AJMC®’s The Center for Biosimilars® about the ways in which patients’ financial stress has spillover effects for clinicians who treat them. Medicine “has limited benefit” if patients cannot afford it, says Oubre, who highlights several studies whose findings show how financial toxicity affects patients. She walks through the process of how her center works with patients to obtain financial assistance. Transparency reduces stress and financial toxicity, Oubre notes. Biosimilars can help increase access to care and lower costs for patients and practices. A study conducted for the Community Oncology Alliance highlighted a 25% increase in patient access when biosimilars are used.

AFTER HOURS

In this segment that appeared during the National Football League playoffs, Sonia T. Oskouei, PharmD, vice president for biosimilars at Cardinal Health, talks with Matthew Gavidia about her memories of being the place kicker for her high school football team. Switching from soccer to football and being the only female player on the team was an eye-opener. She recalls getting used to all the equipment, hearing her name chanted from the stands, and overhearing “what high school boys talk about.” The lessons still resonate today. Oskouei says, “Go for things. Be fearless.”
IBRANCE has been helping to change the story since initial US approval in 2015. See how it has all unfolded at IBRANCEhcp.com
Clinical, Scientific Updates at CCF 2022 Highlight Advances in Cholangiocarcinoma

AS RECENTLY AS 2006, cholangiocarcinoma (or biliary duct cancer) did not have a standard of care, much less advanced treatments. However, the rise of precision medicine and research to create models of how this rare disease works have improved options for the 8000 patients diagnosed each year in the United States, according to the cochairs for the 9th Annual Cholangiocarcinoma Foundation (CCF) Conference, held February 23-25, 2022, in Salt Lake City, Utah, and online.

Lipika Goyal, MD, MPhil, assistant professor of medicine at Harvard Medical School and a faculty member in gastrointestinal medical oncology at Massachusetts General Hospital in Boston, offered an overview of the clinical developments in cholangiocarcinoma (CCA). In addition, Jesper B. Andersen, PhD, associate professor and group leader at the Biotech Research and Innovation Centre at the University of Copenhagen in Denmark, reviewed progress in basic science, especially the development of biomarkers, that is advancing treatment in the disease.

Andersen likened his early years of researching CCA at the National Institutes of Health (NIH) to Sisyphus pushing a boulder up the hill. Fifteen years ago, he said, the landscape was bereft not only of treatments but also cell lines for research. “There was nothing,” he said. Fast forward to 2022, and there have been great strides. Goyal highlighted a tripling in the number of clinical trials, and Andersen pointed to the soaring tripling in the number of clinical trials, and Andersen pointed to the soaring

Goyal is best known for her work on how FGFR resistance develops and how patients can benefit for longer stretches from FGFR inhibitors, a new class of targeted therapy (the first, pemigatinib [Pemazyre], was approved for previously treated patients in 2020). Her talk reviewed recent progress in chemotherapy, targeted therapy, and immunotherapy. She said one reason for progress is that the field has moved beyond characterizing CCA purely by where it is in the body, and instead, looking at each tumor’s mutations. “Now we’re learning to segregate this disease into different molecular buckets,” Goyal said, with the hope that partnering with scientists can yield the same process seen in melanoma, lung, or colon cancer.

Acquisition of tissue through biopsies and donations has allowed investigators to build models of the disease, which Goyal said are now used to develop “more rational clinical trials that have a better chance of helping patients.”

CHEMOTHERAPY. Goyal said the chemotherapy standard of gemcitabine and cisplatin would now be joined by the immunotherapy, durvalumab, based on recent results from the TOPAZ-1 trial (NCT03875235). These data were presented at the 2022 American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI), which found that adjuvant treatment with S-1, an oral fluoropyrimidine derivative, improved overall survival when given after surgery. Additionally, Goyal reviewed a study led by the CCF that seeks to pinpoint which patients need adjuvant therapy after resection. One method being pursued is to collect patients’ blood after surgery for a liquid biopsy, as an analysis for circulating tumor DNA may reveal whether cancer is likely to recur.

TARGETED THERAPY. Reviewing patients’ tissue after biopsy can reveal whether patients have a mutation driving the cancer—and in CCA, there is no shortage of targets, Goyal said. The 2020 breakthrough of achieving FDA approval for therapies that targeted FGFR2 alterations is just a start, she said. It’s what has caused experts in the field to think about CCA differently.

“Over time, we think of the different anatomic subtypes by mutation, as well,” Goyal said. A campaign to reach patients and urge them to ask about biomarker testing is just part of the solution. “The onus is on us, as oncologists, to offer [testing] to all patients, especially because now there are FDA-approved therapies.”

Basket trials, which study mutations across multiple tumor types, have been a boon for CCA research, as it’s still a rare disease despite rising numbers. In some cases, there wouldn’t be enough patients to merit an entire study, but the disease could be studied in an arm or even a few patients in a larger study. Today, patients with CCA can be included in clinical trials involving well-known therapies that have been used to treat other cancers so more is known about adverse events. Goyal offered the example of research with pertuzumab and trastuzumab, HER2 inhibitors that have been used for years in breast cancer, which have now demonstrated tumor shrinkage in CCA.

A first-in-human trial, involving an agent called RLY-4008, produced incredible results in a 35-year-old patient whose tumor was unresectable. He received the FGFR2-specific inhibitor, which caused his tumor to shrink 83%, to the point where he could have surgery. Studies like this are less risky than in the past, Goyal said. “A lot of oncologists don’t do phase 1 trials. Sometimes they [think], ‘Oh, the response rate is 5%.’ But we now have these models—we now have this way of interrogating tumors to figure out what the mutation [is],” she said. “Clinical trials in phase 1 are having much more efficacy than they used to.’”

IMMUNOTHERAPY. Goyal offered additional details on TOPAZ-1, noting that the patients who received durvalumab along with the standard chemotherapy combination had much better survival at 24 months—25% vs 10%. She highlighted the tail on the curve in the results, saying, “There’s a population of patients who are getting significant benefit at 2 years, even though the difference in median survival was not too different.”

BIOMARKER ADVANCES. In his talk, Andersen described how investigators in CCA have emerged from “the Dark Ages” and are catching up in precision oncology, including next-generation sequencing (NGS). Ten years ago, Andersen’s work at NIH led to the first genomic classification prognostic classifier in CCA, which is still used. At that time, Andersen identified that patients with poor prognostic had inflammation and higher levels of EGFR or HER2 expression and KRAS mutations. Those who lived longer had changes in genes involving immune responses, according to Anderson. “Over time, the work led to the identification of IDH1, KRAS, TP53, and other cancer drivers. The identification of the IDH1 mutation led to the 2021 approval of ivosidenib (Tibsovo),” he said. A separate study classified existing drugs by the pathway of their response, with the hope of using off-the-shelf treatments (drugs already used to treat other cancers) to help specific groups of patients with CCA. The number of patients in the study being treated this way grew from 500 to 1500 in just a few years. A half dozen important studies in the past 18 months have focused on single-cell genomics, which examines the individuality of cells, which is made possible by NGS. Andersen said this work helps answer important questions. “For example, with immunotherapy, we can start to understand why some will respond and some will not respond, because it gives an intensified view of the stromal and immune cell niche,” he said. This work also gets into the role of proteins and how cells interact with one another, Andersen added. Biomarkers matter, he said, “because if we really are to make a difference in (CCA), we [must] diagnose the disease much earlier than today.” Andersen explained how there are many types of biomarkers, including prognostic biomarkers, that can monitor both the development of the disease and the response to therapy. This can answer whether it makes sense to continue therapy.
Notably, bile duct cancers are being studied alongside more common cancers in major biomarker studies, such as the DELFI study (NCT04825834) at Johns Hopkins School of Medicine that is examining circulating tumor DNA, Anderson explained. Biomarker research may allow for greater matching of patients to drugs and even prompt investigators to take a second look at therapies that failed poorly in clinical trials. “If we now find the right patients, maybe we can also reuse some of those drugs that are already out there,” he said.

REFERENCES

Shroff: Multiple Targets in Cholangiocarcinoma Make Biomarker Testing Essential

THE ABUNDANCE OF TREATMENT targets in cholangiocarcinoma (CCA) means biomarker testing at diagnosis is “essential” and that next-generation sequencing is needed to clarify a treatment strategy, according to a speaker at last week’s Cholangiocarcinoma Foundation (CCF) 2022 Annual Conference in Salt Lake City, Utah.

Rachna Shroff, MD, MS, associate dean of clinical and translational research and associate professor of medicine at the University of Arizona, offered a review of early-stage research in her February 24 talk, “The Hottest Targeted Therapies on the Horizon for Cholangiocarcinoma.”

TARGETING IDH1 AND IDH2. Shroff discussed a phase 1 dosing trial for Luxo Oncology’s LY3410738, a first-in-class covalent inhibitor of mutant IDH1, found in 20% to 30% of intrahepatic CCA diagnoses. It was described in a May 2021 abstract at the American Society of Clinical Oncology (ASCO) Annual Meeting as offering a “unique covalent binding mode,” increased potency, and a binding site that may work in “second-site” IDH1 mutations. Shroff said the investigational therapy appears to work in a pathway that would allow it to target IDH2 mutations as well. “That’s important here because thus far we do not have something in the clinic available for IDH2 mutations,” Shroff said.

RESULTS SEEN IN HER2. Shroff spent time discussing the MyPathway study (NCT02091141), which is examining currently approved therapies in non-indicated cancers. Results published in September 2021 showed that this approach has yielded results in HER2+ advanced biliary tract cancer when the well-known therapies pertuzumab and trastuzumab were used to treat 39 patients. After a median follow-up of 8.1 months, 9 patients achieved a partial response of 23%. “Clearly, HER2 is targetable,” Shroff said, noting that some patients stayed on therapy for much longer than the median follow-up.

Such a finding “sparks interest and makes us think that there are potentially ways to target this important pathway in biliary cancers.” Zanidatamab, a bispecific antibody targeting HER2, has also shown promise in a phase 1 study, she said. Results for 20 patients with CCA or gallbladder cancer, published at the 2021 ASCO Gastrointestinal Cancers Symposium, showed an overall response rate of 47% for the 17 evaluable patients. Based on these results, the HERIZON-GEA-01 study is proceeding, which will include about 100 patients with HER2-amplified biliary tract cancer, she said.

NRG1 FUSIONS. While rare, Shroff said, neuregulin-1 fusions are “incredibly important to find” because of their behavior. “NRG1 is the predominant ligand in HER3 and, to a lesser extent, HER4,” she said. “This pathway is involved with downstream activation of the HER pathways when you think through tumor proliferation and cellular regulation.”

She explained how seribantumab, an anti-HER3 monoclonal antibody, inhibits the downstream pathway by inactivating NRG1 and limiting HER2 and HER3 dimerization; these actions in turn impact PI3K/AKT and MAP kinase pathways. In addition to the dual activity of the drug, Shroff said, so far seribantumab seems to be well tolerated. It will be further evaluated in a pivotal cohort of the CRESTONE trial (NCT04383210), studying patients without prior Pan-ERBB, HER2, or HER3 targeted therapy. CRESTONE also has 2 exploratory cohorts for patients with prior targeted therapy and those with specific types of NRG1 fusions.

Finally, there is zenocutuzumab, which is being studied in multiple tumor types, including cholangiocarcinoma, through an NRG1 development program. A CCA patient showed a 32% reduction in target lesions, which was considered a partial response, Shroff said.

“ ’There are many potential targets in biliary tract cancers. Upfront biomarker testing...is essential. These rare alterations are crucial to find because now we have trials for these patients. And we may soon have drugs available for these patients.’”

—Rachna Shroff, MD, MS, associate dean of clinical and translational research, associate professor of medicine, University of Arizona

DDIR PATHWAY. DNA damage repair (DDR) studies could be particularly beneficial the 25% to 35% of Asian people who have alterations driving biliary tract cancer, which include the well-known BRCA1/2 genes. “There’s a large component of our patients who may have some potential sensitivity to PARP inhibitors,” Shroff said, explaining that olaparib (Lynparza) is being studied in the ACCRU 1702 study (NCT04042831).

MMD2 AND P53. Shroff concluded by mentioning a study with an experimental treatment that will target the MDM2 oncoprotein, which plays a role in p53 activity. The dual agent BI 907828, a first-in-human study (NCT0449381) of multiple advanced tumor types, “It seems to exert its impact in 2 different ways, through direct targeting of the MDM2-p53 as well as through some immunomodulation of the tumor microenvironment,” she said.

“There are many potential targets in biliary tract cancers,” Shroff said. “Upfront biomarker testing—I’m sure we’ve heard this 100 times already today—is essential. These rare alterations are crucial to find because now we have trials for these patients. And we may soon have drugs available for these patients. Comprehensive testing, looking for fusions, looking for alterations, mutations, amplifications is going to be very important here.”
Comprehensive Cancer Care Adds Value, but Challenge Is Paying for It, ACCC Survey Results Show

**THESE ARE NO BILLING CODES** for more than one-third of the supportive care services provided to deliver comprehensive cancer care, half of the participants in a survey by the Association of Community Cancer Centers (ACCC) reported. The survey results were presented March 4 during the 2022 ACCC Annual Meeting & Cancer Center Business Summit in Washington, DC. Presenters outlined the survey results and offered perspectives on how social workers and pharmacists can support cancer care teams while addressing issues of health equity. Krista Nelson, MSW, LCSW, OSW-C, FAOSW-C, president of ACCC and program manager at Providence Health & Services in Renton, Washington, chaired the session.

“We know that supportive care and comprehensive cancer care (are) the right things to do,” Nelson said. “We know that if we pay attention to the issues that affect patients related to social determinants of health, they will have better outcomes.”

Al B. Benson III, MD, FACP, FASCO, professor of medicine at Robert H. Lurie Comprehensive Cancer Center of Northwestern University in Chicago, Illinois, presented the topline results from the survey, which will soon be published. Benson said the reimbursement challenge puts community cancer practices in a quandary. Comprehensive cancer care required for accreditation can be difficult to fund, he said, because community programs often have less access to philanthropy than academic centers.

“The survey responses demonstrated that programs are not getting reimbursed adequately and in some cases cannot offer these services at all,” Benson said.

The survey was administered from August 2019 to March 2020 with the following results:

- Of the 704 ACCC member programs, 204 responded and completed the survey.
- Of the respondents, 42% were safety-net providers and 33% were participants in the CMS Oncology Care Model (OCM), which has requirements to provide 13 specific services but also makes practices eligible for monthly payments. The OCM ends in July 2022.
- Respondents were asked about 27 specific services required for comprehensive cancer care certification; 50% of the respondents said 10 of these services had no billing codes and 8 had limited or underutilized billing.

Even in OCM practices, Benson said, there was a lack of centralization to gain information on how the practice offered essential supportive oncology services.

**Role of the Oncology Pharmacist**

Ohelekan Ajayi, PharmD, MBA, chief operating officer of Highlands Oncology Group in Fayetteville, Arkansas, discussed the expanded role of the oncology pharmacist on the cancer care team. Pharmacists help patients and physicians understand potential adverse effects and drug interactions as oncology regimens have become more complex. Pharmacists can take an active role in practice management as well as formulary management, including promoting the use of biosimilars to achieve cost savings. But Ajayi said perhaps the greatest focus today is medication adherence, due to the rise in the use of oral oncotics.

“There are still so many other things that pharmacists do in genetic counseling, research,” Ajayi said. “It’s really a very exciting time to be a pharmacist.”

Nelson noted the importance of the oncology pharmacist in research. “If we want to know the clinical trial is valid, we need to know the patients took the medicine,” he said.

**Case for Social Workers**

Making the case for funding social work were Jennifer Bires, MSW, LCSW, OSW-C, executive director of Life with Cancer and Patient Experience at Inova Schar Cancer Institute in Fairfax, Virginia; and Courtney Bitz, MSW, LCSW, OSW-C, director of clinical social work at City of Hope in Duarte, California.

“Patients are coming to us with more and more struggles,” Bires said. “Language differences, unsafe housing, food insecurity, transportation issues all can interfere with a treatment plan or the ability to communicate with the oncologist.”

And it’s not just patients who are stressed. “Medical providers are asked to do more than ever,” Bitz said. When an oncologist is seeing dozens of patients a day, having a social worker available to answer questions can be essential, she said.

The oncology social worker is the primary provider of interventions that can alleviate distress, Bitz said. These are things that can affect not just the patient but also caregivers, and research shows all of this affects health outcomes, she said.

The current focus on health equity makes social workers essential. Sometimes what appears to be an immediate barrier—for example, an individual with a substance use disorder being denied a certain pain medication—could lead to a broader discussion about using community resources and addressing a patient’s larger needs, Bires said.

The challenge with social work is funding the staff, Bitz said. She has developed a model that is being replicated elsewhere for funding social work, but in most cases, social work is paid out of the operating budget. Bires said risk stratification is important. Not every

PRIOR AUTHORIZATION REQUIREMENTS in cancer care have become so burdensome that payers are essentially making coverage decisions one case at a time, according to a panelist in the March 3 session "Prior Authorization: How the Sausage Is Made" during the 2022 Association of Community Cancer Centers Annual Meeting & Cancer Center Business Summit in Washington, DC.

The session panelists collectively said the system needs a lot of work. Andrew Hertler, MD, chief medical officer of New Century Health, said the system was intended not just to make sure treatments are necessary but also to ensure that practices get paid. But other panelists said prior authorization requires practices to make costly investments in personnel and software to navigate payer requirements, and they argued that the shift toward practices assuming risk should make this bureaucracy obsolete.

Prior authorization has become so broken in health care that, “coverage itself is not access,” said John Hennessy, MBA, CMPE, senior vice president and strategist at Valuate Health Consultancy. He explained that prior authorization transactions happen all the time but most are seamless, such as handing a credit card to a hotel clerk who makes sure the bill can be paid before checking in a guest.

In health care, the process is both slow and unpredictable. “Prior authorization at some point was meant to protect people from low-value experiences,” Hennessy said. “When those transactions happen poorly, and they happen with great uncertainty, that value is lost.”

When a practitioner or patient is repeatedly told “no,” they may assume that the services or drugs they cannot have must be really good. Thus, by their behavior, payers are communicating the wrong message, Hennessy said. “That part of the process is broken,” he said.

Lalan Wilfong, MD, a medical oncologist at Texas Oncology, and vice president of payer relations and practice transformation at McKesson Specialty Health, said he’s heard all the payer claims that the next portal will be better—and it’s never true. But most of all, he said, prior authorization represents “inserting an entity into care that’s getting between you and the patient.”

“There’s got to be better solutions,” Wilfong said. Ira Klein, MD, MBA, FACP, vice president of medical affairs and payer relations at Tempus Labs, moderated the panel. Klein, who previously worked for a payer, said there’s an appropriate role for prior authorization—if the payer is administering claims for a self-insured employer, for example, a stop-loss insurer must be informed before a claim gets too large. But when patients receive a diagnosis of cancer and are then told that it’s not clear they can get the diagnostic testing or therapy their doctor recommends, that upsets them.

Are There Solutions to the Current System?

Wilfong said he doesn’t see an issue with documenting the reasons for going off guidelines when that occurs in a small percentage of cases. Regional payers are more willing than national payers to be flexible in giving practices freedom to avoid prior authorization in exchange for assuming risk, he said. Texas has also created a gold card system, which exempts practices from prior authorization if 90% of their claims were approved in the previous 6-month period.

Hertler sees possibilities with artificial intelligence, which would use information from the electronic health record to speed decision-making. But when conversations are needed, Hertler said oncologists should get to speak with other oncologists at the payer level instead of having to explain the need for a drug to a medical director with no background in cancer care.

“It’s a trust-and-verify system,” Wilfong said. Hennessy said prior authorization shouldn’t be used as a hammer to replace the fact that some payers have poor pricing in some regions or at some hospitals.

Finally, Wilfong said, payers have to stop subjecting practices that have assumed risk to the misaligned incentives found across health care. He used an example currently roiling many oncologists: Anthem is telling practices they must use higher-cost rituximab (Rituxan) instead of lower-cost biosimilars.

“Using prior authorization for formulary management is inappropriate,” he said. “We all know exactly what’s going on here.” Practices, he said, will be forced to carry more brands of rituximab and have more refrigerators, and nurses will have to know more formulations.

Hertler agreed, saying that rebates threaten to undermine the ability of practices to manage costs with biosimilars. “The rebates go one place, and someone else is paying the cost,” he said. “If I could eliminate rebates from the world, I would.”

He sees hope in approving bundles of care; for example, a patient with non–small cell lung cancer would be approved up front for diagnostic testing, scans at designated intervals, and a course of treatment.

Panelists discussed abuses with step edits, and Klein sees challenges in the diagnostic space.

“It’s not about which is the best product, but which has the best rebate for the payer,” Hennessy said. “If someone takes offense, I’m sorry, but that’s what’s going on. One of the challenges, as we try as providers of care to take care of patients, is to simplify this process. Sometimes things outside of our control make it a lot more complex. And prior authorization, in some cases, becomes almost a contract negotiation on a patient-by-patient basis.”

City of Hope’s Alvarnas: Payers Must Recognize Cancer Care Is Different

PATIENTS WITH CANCER SHOULD HAVE the same access to precision medicine, clinical trials, and comprehensive cancer care no matter what type of insurance they have, and it should be easier for patients and their families to get needed treatments, according to a hematologist/oncologist and policy leader for City of Hope National Medical Center.

Joseph Alvarnas, MD, vice president of government affairs at City of Hope and chief clinical adviser of Access-Hope in Duarte, California, called for community oncologists and academic centers to join forces to deliver cancer care and highlight the need for a Bill of Rights for patients with cancer, which would highlight gaps that are fueling health care disparities.

Alvarnas spoke March 4 at the closing session of the Association for Community Cancer Centers (ACCC) Annual Meeting & Cancer Business Summit in Washington, DC. The talk was moderated by Alexis Finkelberg Bortiniker, JD, a health care attorney at Foley & Lardner.
CANCER PATIENTS BILL OF RIGHTS

The Cancer Patients Bill of Rights passed the California legislature as a resolution in 2021. Legislation has been drafted that would give the resolution the strength of law. Major elements include as follows:

- **Cancer patients have a right to understand fully their diagnoses** and be informed about treatment options in culturally appropriate and understandable languages.

- **Cancer patients have a right to transparent and timely processes** that ensure access to contracting oncology specialists, diagnostic testing, and accurate interpretations of those tests.

- **Cancer patients have a right to contracting cancer subspecialists** who have expertise in the treatment of their subtypes of cancers when complex decisions are needed.

- **Cancer patients have a right to medical treatments for pain management** and other services that support their overall health.

- **Cancer patients have a right to relevant clinical trials, medical research, and cutting-edge innovation**, including evidence-supported precision medicine.

- **Cancer patients have a right to contracting National Cancer Institute-designated comprehensive cancer centers** and leading academic medical centers for the management of complex cancers that require multiple experts or high-risk or emerging therapies.

Alvarnas said although his work as a clinical and policy adviser is important, what matters most to him is the time he spends with patients at City of Hope, where he is also a professor specializing in HIV-related cancers and hematopoietic cell transplants.

“I’ve had the opportunity to care for a lot of patients who face the cancer journey, where our relationship begins with me saying, ‘You have cancer.’ And once you do that, everything that patient and that family knew before that moment is irrevocably changed by those words,” Alvarnas said.

What happens next, he said, determines whether the patient and family can be “restored to wholeness,” or whether they will experience “a nightmarish, disconnected experience of what represents the worst attributes of our health care system.”

A theme of the ACCC meeting that resonated strongly, Alvarnas said, is the idea “that patients and families are what really matters.”

He offered examples of where care has fallen short, telling the story of a Spanish-speaking patient who had been treated for 10 years but did not realize that he had leukemia. Another patient lost access to the care she’d been receiving because of changes to her managed care plan. She had to come up with a workaround to stay on her regimen of immunosuppressive drugs.

“Patients and families shouldn’t have to work around the edges of the system in surreptitious ways to ensure that they stay alive,” Alvarnas said.

Yet these stories are becoming more common in the era of narrow networks; despite incredible scientific advances, Alvarnas said, disparities in cancer care are widening.1

The American Association of Cancer Research (AACR) 2020 progress report stated that 34% of cancer deaths among adults aged 25 to 74 years in the US could be prevented if socioeconomic disparities were eliminated.2

Last year, City of Hope officials became frustrated by these gaps in payer coverage—especially in California’s Medicaid system, Medi-Cal. They worked with advocacy groups to get resolutions passed in the legislature, and in August 2021 the California State Assembly unanimously passed the Cancer Patients Bill of Rights (Figure).

The quest now, Alvarnas said, is to put these ideas in a statute that would have real impact.

“What would a bill of rights look like?” he asked. It would include the right to culturally appropriate care, ensuring that treatment options are fully explained in a patient's own language, he said, and it would ensure transparency, creating better processes for engaging oncology specialists with the skills to understand complex genomic testing results that can guide treatment.

Patients’ rights would include timely access to an oncologist after a diagnosis. “There's something morally repugnant about building a system saying that people have coverage, but that coverage doesn’t translate into access,” Alvarnas said.

It would give patients “the full breadth of opportunities” to get care in a community setting; he said, but also access to specialized care—for example, if their disease required chimeric antigen receptor (CAR) T-cell therapy or other cutting-edge treatments. And patients should be able to return to a community setting “in a way that doesn’t involve lifting Heaven and Earth to make it happen,” Alvarnas noted.

For all the discussion of doing more to help vulnerable communities—and end underrepresentation in clinical trials—patients often have precious little to say about their own care whereas payers make all the rules, Alvarnas said.

“What's missing in too many conversations is the way in which patients and families can resume agency in their lives,” Alvarnas said. The Cancer Patients Bill of Rights was seen as a way to put patients—not cost cutting or other priorities—back at the center of the discussion.

In the California Assembly, he said, the resolution had unanimous support.3 But, Bortiniker asked during the talk, what makes this the best approach to address lack of access?

Alvarnas said something must be done to address the growing gaps in care between groups as innovation proceeds. Cancer mortality has decreased 31% since Alvarnas was a resident more than 30 years ago, “and over the past 2 years, if you look at [American Cancer Society] reports, cancer mortality has decreased by the greatest decrements ever seen,” he said.
“Innovations have had an outsized impact upon the needs of patients with cancer and the promise of what that cancer journey can look like,” he said. “On the other hand, when I look at those statistics and I look at things like the AACR 2020 report, describing health disparities, it’s clear that those great advances have not been equally or fairly or equally realized by patients who bear the burden of cancer.”

Cancer care professionals, he said, must turn to the policy arena to fix this problem. “We have to get out of our offices, we have to get out of our centers, and work with partners across a whole bunch of different industries but also with policy makers, because I know that policy makers are working in well-intentioned ways to improve access to care and to improve coverage,” he said. Efforts such as the Cancer Moonshot 2.0 show that fighting cancer remains top of mind for political leaders. “But unless oncologists and hematologists speak out, the right solutions may not rise to the top.

Too many unique needs of patients with cancer “get lost in the mad dash to achieve grand overarching designs,” he said. Working with legislators to articulate their needs would be a “grounding moment.”

Alvarnas said he found it striking how much California’s legislators identified with City of Hope’s ideas. Most lawmakers knew of a friend or family member who had become exasperated by the current system. They understood that “cancer can be dehumanizing, and that the moment of realizing that you’ve been diagnosed with cancer is so disempowering,” he said.

Because the first step in California was a resolution, the focus was on articulating core principles of accessibility, scalability, and patient experience rather than numeric goals. That will come, however. City of Hope has formed partnership with minority health care groups, and its work with employers suggests there are many allies in this cause.

Part of the mission, Alvarnas said, is “increasing expectations.”

Frequently, patients want referrals to academic centers but their requests are denied by a managed care provider, Alvarnas said. “Fundamentally, we don’t want clinicians to be caught in a position of being subjected to a model that sometimes tries to achieve efficiency through strangulation of resources,” he said. “That the idea that you can reverse engineer care to suit a certain preconceived notion of how much health care can cost is a very dangerous path to go down.”

This view extends even to CMS, where the Oncology Care Model (OCM) was judged based solely on whether it saved money within just a few years rather than on the efforts it spurred in practices to transform care delivery—a process that comes with a steep learning curve. The delivery system needs to start with the community physician but offer flexibility to refer patients to academic centers if their cases are especially complex or if doing so could offer access to a clinical trial, Alvarnas said. Clinicians can’t be gatekeepers for the insurance company, he said.

“The system has to be more scalable [and] suited to help serve patients based upon their needs, as opposed to being constructed with these rigid barriers that aren’t based upon clinical insights,” Alvarnas said. Too many judgments by insurers are not based on clinical guidelines and don’t reflect how doctors want to manage cancer, he said.

Data in California show that Medicaid beneficiaries have worse outcomes than others with cancer and that patients covered by Medicaid are less likely to have care that follows guidelines. With this in mind, City of Hope created the campaign “Cancer Care Is Different” to empower patients and families “to have the best outcomes possible.”

What about cost? Alvarnas said that much of the policy focus—and resulting denials by payers—centers on ensuring the solvency of the Medicare trust fund or making sure state Medicaid systems stay within a budget. Too often, however, this results in the wrong care being given and the overall cost being higher than it would have been if the right therapy had been given initially, he said.

“In fact, when we’ve done value analytics around the work at AccessHope, there is a return on investment to delivering the right care early on,” Alvarnas said. Cases such as these offer power when legislators see them—but the lawmakers need to hear from patients, not just clinicians, he said.

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COMMENTARY

Redefining Cancer Care: Putting Equity, Quality, and Patients at the Center

Sachin Sengupta

THE CANCER JOURNEY is different for every person, and intertwined in this experience is the quality of care available to each patient. I learned this first-hand: My grandfather was diagnosed with prostate cancer a few years ago, and he has recovered. Although this experience was hard for our family—and especially for my grandfather—he was fortunate to receive quality care that was digestible for him. While fluent in English, my grandfather is an immigrant and has been deeply involved in the Indian community throughout his life. “My care was efficient, and while hard at times to endure, very easy to understand,” he says. I will forever be grateful for the many doctors, facilities, and treatment plans offered to my grandfather, but I am mindful that not everyone receives this same level of care. For many patients, differences in culture and language, distance from treatment, and other barriers can impact the quality of care. Others suffer when insurance companies will not cover care at advanced facilities or approve therapies that their doctors recommend. After studying public health at the University of California, Berkeley, I have come to see just how large a role social epidemiology plays in the battle against both communicable and chronic disease. One thing is clear: Equitable care does not yet exist.

Joseph Alvarnas, MD, Professor of Hematology at City of Hope Comprehensive Cancer Center (Los Angeles, CA), has shared insights that arise from his advocacy to improve experiences for cancer patients across the United States. “For many models in health care, the ability to think about patients in general and standardized ways may help to present a path toward better care and more efficient care. Broadly based pathway care for patients with diabetes, hypertension, and hyperlipidemia may be powerful in improving population health. In the domain of cancer care, however, individualized care models are not only wrong, but it can also lead to low-value care, worse patient experience, and inferior outcomes,” Dr Alvarnas explains.

The fight to improve cancer care includes aspects of both equity and quality. Over the past decade, health insurance coverage has been expanded to millions of previously uninsured Americans, but there is evidence that not every patient has the same access or the same quality of care. Dr Alvarnas notes that the quest to improve care and care equity, it is essential to through 4 essential pillars, and over time, drive change to make cancer treatment more efficient and patient centered. The pillars are:

1. Patient- and family-centered care that begins with a focus on individual needs, including goals of care;
2. Leveraging the use of precision medicine to design treatment around individual genomic data, comorbidities and functional status in order to ensure the best outcomes for patients;
3. Giving all patients access to a robust set of clinical trials, no matter where they live; and
4. Investing in the equitable care of underserved communities.

Equity and Social Determinants of Health

While “equality” means that each person is given the same opportunities and resources, “equity” recognizes that each person starts from different circumstances, and that resources and opportunities should be allocated as needed to achieve fair outcomes. As medical treatments and technologies improve, it is easy to downplay the importance of achieving equity, especially in cancer care.

The most important drivers of inequity in cancer treatment are social determinants of health (SDOH). These refer to factors such as a person’s overall health, economic stability, social community, and level of education, all of which can significantly affect access to quality health care. These SDOH carry with them the many inequities present in American society. A 2020 progress report from the American Association for Cancer Research (AACR) revealed that disparities in care mostly affect minorities and those from groups with lower socioeconomic status, due to a lack of access to care, lack of education surrounding treatment, and the rise of narrow provider networks that limit patient choices. I hope to shed some light on the hard truth that disparities in cancer care exist, and that only through efforts by both those in power and their constituents can we alleviate the stress on those battling cancer.

Differences by race are among the most important—and concerning—factors that contribute to cancer health disparities in the United States. Data from the AACR report show that 21% of Black Americans were living below the federal poverty level in 2018, along with 18% of Hispanic Americans and 8% of non-Hispanic White Americans. Closely related are the levels of uninsured in each group: 10% of Black, 18% of Hispanic, and 5% of non-Hispanic White Americans were uninsured as of 2018. You don’t have to be a public health expert to realize that such stark differences are tied to disparities in quality and access to cancer care.

Some may propose a simple solution: Expand access to insurance. However, research has shown that access alone is not enough to close the equity gap. A key article in the Journal of National Comprehensive Cancer Network (NCCN), explored the connections between race, insurance coverage, and quality of care. The authors concluded that Black patients and those on Medicaid were “less likely to receive guideline-concordant medications compared with White patients and those who had managed care insurance plans.” In fact, the study results showed that “having Medicaid also decreased a patient’s likelihood of receiving a therapy endorsed by NCCN; this effect was seen in breast, prostate, colon, rectal, gastric, and liver cancers.”

Thus, having insurance does not guarantee access to quality care. A 2022 paper from Kaiser Family Foundation reported that members of minority groups consistently experienced lower rates of cancer screening, diagnoses at later stages, and longer treatment delays. Depending on the cancer, this work also concluded that minority patients may be less likely to receive guideline-recommended treatment.

Patients who are poor or live in rural areas may also lack access to local care and transportation. The transportation gap is especially pronounced if one needs access to one of the 52 National Cancer Institute-designated Comprehensive Cancer Center (NCICCC) located across the United States. In order to most effectively serve patients with cancer, we need to build systems that are scalable to meet patient needs wherever they are. Unfortunately issues like narrow networks, transportation, and socioeconomic status (including financial resources) may limit that access and compound the complexity of the patient journey.

Clinical trials, which may offer the best chance of survival, are out of reach for many patients. A study by Columbia University and the American Cancer Society looked at 13 studies involving almost 9000 cancer patients and found that “(more than) half of patients didn’t have a trial available to them at their institution…and almost a quarter were ultimately deemed ineligible” when they applied for a trial. One can only imagine that SDOH play a role.

Having insurance does not guarantee access to quality care. A 2022 paper from the Kaiser Family Foundation reported that members of minority groups consistently experienced lower rates of cancer screening, diagnoses at later stages, and longer treatment delays.

The Emotional Toll of Cancer

Aimid tangible barriers to quality care, the underlying mental health issues that cancer patients face should not be overlooked. The fight against cancer can be just as much emotional as it is physical. It is estimated that “16% to 25% of cancer patients develop depression…and that doctors do not recognize about 35% of these cases and many patients remain untreated.” This risk of depression rises if patients receive care that is subpar, especially care that does not align with NCCN guidelines. While some mental health symptoms can be treated with therapies, the most effective support is a strong social network. As noted by Edwards and Clarke in Psychooncology, “a lower incidence of depression is associated with the ability of patients...to freely communicate information to their physicians and family members.”

The results of multiple studies, however, have shown that patients from lower socioeconomic backgrounds may have a harder time discussing with doctors the physical and psychological issues they face. Whether this is due to issues of health literacy, or a reluctance to engage providers in more directed conversations regarding treatment alternatives, more resources are needed to improve health care literacy, built trust amongst underserved groups, and create community-based resources for advancing patient agency throughout the cancer journey.

Lack of equity in cancer treatment is multifaceted and demands a more complex solution than simply “expanding coverage.” Barriers such as a patient’s type of insurance, travel to comprehensive facilities, and poor health literacy rates—driven by and reflective of SDOH—have put the highest-quality cancer care out of reach for many, and these barriers will continue to claim lives if nothing is done.

What is the solution? One estimate posits that more than 34% of cancer-related deaths could be prevented if disparities in socioeconomic status were alleviated. Although these challenges do not live solely within the health system, there are some health care system-specific steps that can be taken now. An upstream approach that puts more resources into health education at the elementary or high school level would ensure that over time, we can improve access to care, understanding of treatment, and coverage to the individuals most in need. For far too long, science has been separated from emotional underpinnings...continued on SP122
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in the hopes data-driven approaches can resolve the underlying social/economic issues in our society. However, science often fails to account for the needs of specific communities. What may be beneficial for one group may not be feasible for others. Expanding coverage and creating new treatments, as useful as they may be, can at times overshadow the issues that specific communities face when it comes to treating cancer.

Data from HHS show that as of June 2021, 31 million people have coverage either through the Affordable Care Act's Health Insurance Marketplace or through Medicaid expansion, and since then numbers have only continued to grow.10 While this expansion in coverage has led to improvements in screening and better treatment for chronic conditions, it masks the difficulties in keeping the quality of cancer care standardized across all US medical practices. Despite progress in reducing cancer mortality, evidence shows that patients from minority groups frequently receive care that is of poorer quality than the care White patients receive.11 Too often, minority patients do not receive care that aligns with NCCN guidelines.1 These are issues that need to be brought to light. Only through iterative collaboration amongst community oncologists, academic centers, patients, families, communities, payers, and policy makers can these disparities be highlighted, and cancer care redefined. ●

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REFERENCES

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Even CMS’s Center for Medicaid & Medicare Innovation (CMI) has fallen short, and Alvarens sees the agency as less willing to experiment with new models than many employers.

Treating patients and families with humanity is essential. “When you talk about better outcomes, it isn’t the patient waiting in more lines or having to go through 30-day increments of having to appeal access to care or site of care...,” he said. “It’s not in patients experiencing financial toxicity. It’s not in patients navigating the spaces in between where something should be delivered here, something else should be delivered there. That’s the worst conceivable possible system.”

Value, he said, must be centered around the needs of patients and families who are living with cancer day to day. “This is where I get a little bit flustered— I read through the CMMI assessment of the OCM, and conclusion number one, it wasn’t save money. All I can think is ‘My God, you learned nothing.’”

The work that occurred at the practice level to keep patients out of the hospital or offer navigation help or survivorship was completely lost, he said. “CMS didn’t notice,” Alvarens said. “There’s no value described in that report. I think if your primary conclusion is that (OCM) was a failure because it didn’t save money, you weren’t paying attention.” ●

REFERENCES

From Getting Paid to Managing Burnout, Panel Examines Future of Community Oncology Care

VALUE-BASED ONCOLOGY CARE is here to stay, with or without leadership from CMS, because commercial payers and patients have seen its benefits, according to leading practice administrators who took part in the March 17 discussion, “Building/Designing the Community Oncology Practice of the Future,” during the 2022 Community Oncology Conference, presented by the Community Oncology Alliance.

Barry Russo, MBA, CEO of the Center for Cancer and Blood Disorders, moderated the session, which featured Glenn Balasky, executive director of Rocky Mountain Cancer Centers; Jeff Vacirca, MD, CEO of New York Community Oncology Alliance; and Emily Touloukian, DO, president of Coastal Cancer Center.

Russo asked for predictions on the future of reimbursement, and Balasky said CMS’s decision to let the Oncology Care Model (OCM) expire without a
Revenue cycle management is the lifeblood of our practice,” Russo said. After years of experimentation with the OCM, some practices were taking steps such as paying for advanced care planning. Data collection from OCM patients will help practices show payers how value-based care worked in their favor, he said.

The challenge now will be finding ways to retain momentum. “We’ve got to keep on this path,” Balasky added.

Vacirca said the next step is to work with employers to demand movement away from FFS toward payment for episodes of care. Among insured patients in New York, he said, 90% are dealing with a payer that is a third-party administrator (TPA) of their plan—and in these cases, there’s no incentive to cut premiums.

“If they drive premiums down as the TPA, they make less money,” Vacirca said. “You’ve got to get to the employers, because the employers have no clue whatsoever that the payers are working contrary to what are their best choices.”

Together with reimbursement frameworks are the challenges of prior authorization, which clinicians report are more cumbersome than ever. Balasky said his practice just hired a staff member to work solely on payment for genetic testing, because so many patients have been billed for this despite the growing role of precision medicine in cancer care. Vacirca said he’s interested in how Texas’ new “gold carding” law could set a standard that eliminates prior authorization for services. “The challenge I see, from my conversations with the insurance industry, [is that] they have built a piece that they can’t untangle,” he said.

Unfortunately, Balasky said, too many payers have created incentives with brokers to build in utilization review and other steps that prevent quick payment for services. “The challenge I see, from my conversations with the insurance industry, is that they have built a piece that they can’t untangle,” he said.

Russo recalled a conversation with Vacirca on how this system forces practices to add staff and systems to keep payments flowing despite the barriers. “Revenue cycle management is the lifeblood of our practice,” Russo said.

SITE OF SERVICE. Russo shifted the discussion to a trend that took hold during the pandemic, in which practices are pressed to offer infusion to patients’ homes. The panelists agreed that this creates safety risks if physicians see patients less frequently, and that it’s an inefficient use of nurses’ time.

“It’s not really clear that there are actually cost savings, to the system or to the patient,” Touloukian said. When a patient is in the clinic, they are evaluated for iron levels and clinicians gain more insight into adverse events, which help prevent hospitalization.

“Something that community oncologists really excel at is bringing that sort of home experience into the clinic,” Touloukian said. “It’s one of our strengths.”

Both Balasky and Vacirca said the trend is rooted in a lack of attention to total cost of care and battles over which parts of cancer care are charged to a patient’s medical plan vs a prescription plan.

“In vertically integrated systems, it’s another way for the pharmacy benefits managers [PBMs] to bring in infusions onto themselves, to charge them back to the employers for huge amounts of money and then not be transparent about any of it,” Vacirca said.

Russo then asked about the future of telemedicine, and Touloukian said it will remain part of the landscape but perhaps be used differently than it was during the pandemic. For example, the ability to consult multiple family members on a telemedicine call to discuss a cancer patient’s treatment plan can be beneficial—Touloukian has helped members of her own family this way.

Remote monitoring will also evolve, as some patients appreciate extra contact while others don’t want to be bothered. The value of such contacts must be made clear in advance, Balasky said. Vacirca pointed out that remote monitoring is a more modern term for all the times physicians have been interrupted with questions and issues that come up between visits.

For years, doctors called patients after 5 pm to go over test results. “You’re missing your kids’ ball games, missing [your kids’] ballet [classes], and getting home at 8 o’clock,” Vacirca said. “We’ve done this our whole careers. Finally, there’s an opportunity for us to actually continue what we’re doing, to have that patient connection, to see the patient at the same time and get paid something for the work we do.”

“One of the things we learned through the pandemic was that we needed a better way to communicate with patients.”

—Barry Russo, MBA, CEO, Center for Cancer and Blood Disorders, Fort Worth, Texas

MARKETING COMMUNITY ONCOLOGY. As consolidation and vertical integration drive up costs elsewhere, community oncology needs to find new ways to highlight its value.

“One of the things we learned through the pandemic was that we needed a better way to communicate with patients,” Russo said. Digital solutions to telling the story are necessary, as new competitors such as CVS Health and Optum enter the market. Vacirca said other community practices are being seen as collaborators and perhaps future partners, given the headwinds. “How do we grow and become more successful together?” he asked.

Balasky sees the major academic centers as offering complexity at a time when consumers want more simplicity. But community oncology needs to do more to communicate its value within local markets, and Russo agreed that more must be done with tools such as search engine optimization and social media to make sure practices get noticed.

There’s a good story to tell, Vacirca said, but until now, lack of transparency has made this difficult. “We just got transparency on premiums,” he said. “There’s no transparency on payers. The employers are waking up and realizing this.” Even his own practice is learning its lesson. For years the group had coverage through UnitedHealthcare; this year, after a switch to self-insurance, “the first thing we did was take the PBM out of the equation” and begin to manage drugs directly. “As an employer, it took 20% to 30% off the top.”

PERSONNEL AND BURNOUT. Russo said the pandemic has offered new lessons to oncology practices, including the value of well-being. He spent the final minutes of the session on mental health among clinicians and the difficulty practices have finding staff. The generation of physicians trained in “work, work, work until you drop dead” is giving way to a new one that demands more attention to family and life priorities.

Mental health is “incredibly important” in community oncology, Touloukian said. “It’s going to look different for everybody,” she said, “not just from practice to practice but for each individual.”

Practices cannot passively wait to hear from staff members about scheduling problems or the need to work from home—they must go out and actively engage with the staff, Touloukian said. Russo said his own view on the subject
Pilot Projects to Reduce Cancer Care Disparities Deserve Support, Speakers Say

**PRACTICE-LEVEL EFFORTS** to reduce cancer care disparities should be funded, because they offer “the only path forward” in achieving health equity, according to the head of a nonprofit that offers support services and financial assistance to patients.

Patricia J. Goldsmith, CEO of CancerCare, said a pilot project by Carolina Blood and Cancer Care Associates (CBCCA), centered in Rock Hill, South Carolina, should be replicated to reduce the number of cancer deaths that can be tied to patients’ income, housing situation, or other factors known as social determinants of health (SDOH).

Goldsmith appeared at a panel discussion on reducing disparities in care at the 2022 Community Oncology Conference, presented by the Community Oncology Alliance (COA). COA president Kashyap Patel, MD, discussed the initiative at CBCCA, where he serves as CEO. Early results from the project, called No One Left Alone (NOLA), appeared recently in *Evidence-Based Oncology™*, a publication of *The American Journal of Managed Care®*. 1

In a yearlong pilot, CBCCA dedicated 2.5 full-time equivalent staff to helping patients with cancer secure free drugs or financial assistance for out-of-pocket costs, if they met income requirements. The initiative raised $1.7 million in various forms of financial assistance, helping nearly half the patients treated at CBCCA. The 154 patients who received help had a median household income of $38,766, well below the US and South Carolina median levels. 2

Patel said NOLA has already moved into stages of the project that will help patients gain access to next-generation sequencing (NGS). Several speakers at COA said NGS presents unique reimbursement challenges, despite the mounting evidence in support of precision medicine. In the long term, Patel said, CBCCA will work to improve diversity in clinical trials; he said smaller practices like his are often excluded from participation, despite their ability to reach underrepresented populations.

“This is exactly what we need,” Goldsmith said. No single initiative will address all SDOH issues in cancer, so “we’re going to have to demonstrate results in small but very impactful ways.”

Nicolas Ferreyros, who serves as COA’s managing director for policy, advocacy and communications, moderated the panel and highlighted a study that COA undertook with Avalere Health; results were published ahead of the conference (see Cover). That study, which followed earlier work that documented the drop-off in cancer screenings during the early months of the COVID-19 pandemic, showed that screening rates did not recover evenly, and some minority groups still have lower screening rates than they did before the pandemic.

Ferreyros guided Patel through a discussion of how the quest to address disparities became a central focus for COA during Patel’s tenure as president. Patel said that the death of his father in 2019, combined with turning 60 years old, caused him to think more deeply about serving those with the greatest need. “In the last quarter of my life,” Patel said, “I decided to tackle disparities….This was almost like a higher calling.”

Ferreyros also highlighted data in a 2020 report from the American Association of Cancer Research that found that 34% of all cancer deaths are due to disparities. 3

“Now, 34% does not sound like a huge number,” Patel said. But in absolute numbers, it translates to nearly 225,000 Americans each year. Those statistics should shock most people, but they don’t get enough attention, he said. 3

One piece of COA’s effort to reduce disparities focuses on cancer screening. COA has collaborated with CancerCare and other partners on “Time to Screen,” which puts a focus on underserved groups. Susan Sabo-Wagner, RN, BSN, OCN, clinical director of Oncology Consultants in Houston, Texas, shared how materials were translated into Spanish, Vietnamese, Chinese, and Haitian-Creole. 5

Sabo-Wagner’s practice is using artificial intelligence (AI) to go a step beyond waiting for patients to miss an appointment or a treatment to learn that there’s a social or financial barrier to care. Building predictive models will identify which patients are likely to have problems with treatment adherence, she said.

“We have our advocates reaching out to patients with the resources,” said Sabo-Wagner, and then she organizes the follow-up to ensure that patients connect with available help. Using AI demographic data, and a survey tool allows the practice to “pinpoint what we should be doing for patients, ahead of what we need to do.”

Patel agreed that cancer clinics often have no idea how SDOH affect patients unless they ask. He shared the story of one patient who had been living out of his car, but until the staff asked about his housing status, they were unaware of this fact.

Patel challenged the pharmaceutical industry to move beyond “the ivory tower” and ensure that community oncology practices have more research opportunities. Only then will the population in clinical trials start to represent the country’s diverse population, he said.

“The current model has failed,” Patel said. For instance, nearly a third of Americans have diabetes, he said, and these are the patients who show up at his clinic with cancer. Yet too few patients with comorbidities are permitted to take part in studies.

Goldsmith, who worked in academia before leading CancerCare, said she found it eye-opening to learn how big a difference small grants and support services can make to a patient with limited means. She commended Patel for creating NOLA without outside funding, forging ahead “because of your passion.”

REFERENCES


**Why Measures Matter—and How to Inspire Cancer Practices to Use Them**

**QUALITY MEASURES ARE** the lifeblood of practice transformation, but learning which ones make a difference—and how to use them to drive change—is as much an art as a science, according to 3 oncology care leaders who discussed the topic on March 18 at the 2022 Community Oncology Conference, presented by the Community Oncology Alliance.

Panelists Stephen Schleicher, MD, MBA, chief medical officer at Tennessee Oncology and medical director for value-based care for OneOncology, and
Lalan Wilfong, MD, vice president for payer relations and practice transformation at The US Oncology Network and a longtime medical oncologist at Texas Oncology, joined moderator Ali Rahman, MBA, MHA, practice administrator for Oncology Consultants in Houston, Texas, for a session that covered gathering data and deploying it within a practice.

As Rahman explained, numbers on a dashboard don't drive change all by themselves. He described a "transitional phase," which is as much about conversations as the data. Physicians, nurses, and other staff must be educated on why data collection matters and how it can drive better patient care and improve the bottom line. It's not a process that happens overnight, the panelists said.

As Schleicher put it, getting data into a dashboard is the easy part, but "the hard part is to get people to do something different."

The panelists agreed that starting out slowly, with a focus on a few key measures that can identify "outliers," is a good way to get buy-in without overwhelming care teams.

Schleicher and Wilfong stressed the importance of involving diverse stakeholders from across a practice. Wilfong said deciding who needs to be involved is important, and so is strong leadership. "At times, leadership has to say, 'I know this isn't pleasant, but we have to do it,'" he elaborated.

What happens, Rahman asked, when there is disagreement?

Schleicher advised that those who will be affected by a quality measure should have opportunities to weigh in on how it will be used. A given metric may be very important to some staff members and less important to others.

Wilfong said some metrics—such as how long it takes to schedule patients for appointments—must be monitored every day. But for other measures, including those that affect physicians, it may be better to measure less frequently, so that a single uncommon event such as a patient death doesn't skew results. Schleicher said the question of how frequently to report metrics to fellow clinicians and the staff is one he's still trying to answer.

"We've settled on quarterly for an extensive report," Schleicher said.

Wilfong agreed: "Physicians don't want stuff in front of them every single day."

Rahman explored the merits of positive and negative reinforcement. Sending out emails that show physicians how they rank among their peers will often spark change among a group that is competitive by nature. But tying quality measures to compensation, such as a portion of the annual bonus, may be necessary.

Bonuses can be added dollars if quality measures improve, but they can also involve taking money if measures are poor. Wilfong said sometimes that's what gets physicians to pay attention. In other words, he continued, "for some doctors, if you take $1 away, they completely freak out."

Schleicher spoke at length of the care he takes in communicating subpar results. The process shouldn't be about shaming people, but about having a conversation on why an individual physician is using a more expensive medication when a cheaper one will work. He said it's important to realize that for many physicians, being compared with their peers is a relatively new concept.

"Before OneOncology had the tools to do this," Schleicher explained, most clinicians had no idea how their resource utilization compared with that of others, and no clue "whether they were average or an outlier."

Wilfong said US Oncology did an exercise that compared physician behavior in the context of a fee-for-service environment vs. that of a risk-based model. Doctors went from thinking about an extra PET scan as something they could bill for to something that might cost them money. "As we take on more risk, the paradigm changes," he said.

Schleicher emphasized the need to take things slowly, to balance driving change with ensuring that the data are accurate. For instance, if a physician

is told he is an outlier in a metric and the data turn out to be wrong, trust is damaged. "Don't send anything out if you're not 100% confident," he said. "If the quality is not there, it's really hard to make up for it."

Prior Authorization Woes Could Lead to Lawsuit, Former AMA President Says at COA

Prior Authorization in Cancer care has become so burdensome, costly, and harmful for patients that health plans and pharmacy benefit managers (PBMs) could face a lawsuit, the former president of the American Medical Association (AMA) said during a session on March 17 at the 2022 Community Oncology Conference, presented by the Community Oncology Alliance (COA).

Barbara McAneny, MD, CEO of the New Mexico Cancer Center, who served as AMA president in 2018, said the AMA has engaged a law firm to take on the issue of curtailing prior authorization. Oncologists say prior authorization abuses have increased with the rise of vertical integration among health plans and PBMs, causing treatment delays and overriding doctors’ attempts to use innovative therapies.

McAneny was a panelist in "Battle Royale: Payer Utilization Management vs Physician-Directed Medicine,” which was moderated by Debra Patt, MD, PhD, MBA, vice president of Texas Oncology, and also featured Leslie Busby, MD, chair of The US Oncology Network Pharmacy and Therapeutics Committee and an oncologist at Rocky Mountain Cancer Centers.

Although the oncologists said practices have had problems with prior authorization for years, McAneny noted that the situation has reached a crisis and is fueling clinician burnout. A recent demand that cancer patients be given an older, cheaper formulation of intravenous iron may be the example that propels litigation. For savings of $5 a unit, she said, patients have been forced to receive iron dextran (Infed), an iron replacement formulation known to cause more severe reactions than newer products.

The position of some payers, according to McAneny, is that “Infed is good enough—good luck with that iron reaction.” Although she and Patt agreed that going to court is never the first choice, sometimes it’s necessary. Finding the right plaintiff is the next step, McAneny said.

Both Patt and McAneny shared some alarming statistics on the burden that prior authorization creates for practices. Patt shared results of an AMA survey showing that 40% of physicians have staff who work exclusively on prior authorization, and that 93% of physicians report that patients have seen care delays. Patient harms are real, Patt said: “34% of physicians report that a prior authorization process has led to a serious adverse event [AE] for a patient in their care.”

McAneny’s practice did a study that examined the time spent getting patients through the prior authorization process. The mean time spent waiting on hold for a single infusion approval was 18 minutes. “Now, keep in mind that we’re paying these people about $20 an hour. So that’s about $6 to sit on hold, which is really a good use of health care resources,” she said sarcastically.

Sometimes calls went quickly; in other cases, staff were on hold up to an hour. The mean number of days to get chemotherapy approved was 10.5 days. "That’s a lot of time for patients," McAneny said.

Busby said he sees similar problems. In the past, delays in getting a new therapy approved were normal, but today, there are delays even for
well-established regimens. The rise of "fail-first" policies—which require patients to take older, less effective treatments before trying new ones with demonstrated superiority—is harmful in cancer care, as evidence shows that using the best therapy first leads to the best outcomes.2 "That first treatment is very important," Busby emphasized.

When a patient who takes an older chemotherapy starts vomiting, a cycle is established that can be very difficult to control. The fail-first approach is "pen-ny wise and pound foolish," Busby said. For practices that have value-based agreements in place that focus on total cost of care, he said, "1 hospitalization or 1 [emergency department] visit wipes out any savings."

Patt, a breast cancer specialist, reported that payers sometimes treat all CDK4/6 inhibitors as if they are the same, even though their AE profiles may vary, especially for patients with underlying health issues. "Just because there are 3 doesn't mean they are all equal," she said.

Patt has seen cases in which a patient on a CDK4/6 inhibitor ends up taking the drug for 3 months, then must skip a month because of payer delays in renewing their prescription. It's impossible to expect the drug to be as effective when this happens.

A practice-level study found that the average time on hold for a staff member to reach someone at an insurance plan was 18 minutes. "Now, keep in mind, we're paying these people around $20 an hour. So, that's about $6 to sit on hold, which is a really good use of health care resources."

—Barbara McAneny, MD, CEO, New Mexico Cancer Center, Albuquerque, New Mexico

McAneny said a root of the problem is the lack of connection between health plan officials managing the medical side of costs vs those who are managing pharmacy benefits. The PBMs may be rewarded for "savings" because the costs of their decisions are borne elsewhere. "They don't really bridge that gap very often," she said.

Too often, health plans don't understand the unique needs of cancer patients. Health plans try to tightly manage use of scans, McAneny said, because they worry about overuse in treatment for chronic back pain. But for a cancer patient, back pain can indicate that their disease has progressed, and scans must be timely.

Use of fail-first as a tool to enforce a restricted formulary is spreading, according to Busby. He said payers refer to barriers as "speed bumps," because they know a certain number of physicians simply won't push for a preferred treatment.

Even biosimilars are not exempt: Some PBMs demand that oncologists use a specific biosimilar even if the practice is using a different one for the same reference product. In these cases, patients receive appropriate treatment, but practices are "afraid that they won't pay you for that treatment."

What can be done? "There is a real role for advocacy," Patt said. Reaching out to elected officials and lobbying partners is essential to heighten awareness, she stated.

Transparency will be essential to reform prior authorization, McAneny said, because it's clear that rebates and financial incentives are driving mandates instead of what's best for patients. Payers and PBMs should not be allowed to dictate care based on what's "economically advanta-

geous to the insurance company," she said. Currently, she opined, "it's all about the money." 

REFERENCES

In Letter, COA Urges CMS to Do More to Rein in PBM Fees

THE COMMUNITY ONCOLOGY ALLIANCE (COA) has urged CMS to take stronger action to regulate pharmacy benefit managers (PBMs), saying that without action, these entities will “abuse loopholes” despite the agency’s recent effort on “direct and indirect remuneration,” or DIR fees.

In a March 7 comment letter on CMS’ proposal to regulate PBM fees, COA leaders warned that without a stronger rule, the proposal’s positive effects could be erased. Specifically, COA recommends that all reimburse-ment provided to pharmacies should not be lower than the acquisition cost of the drugs dispensed.1

The issue, COA states, are DIR fees, a comparatively new type of revenue stream to PBMs imposed on independent and retail pharmacies, as well as pharmacies that are part of specialty cancer and urology practices. CMS has stated that the fees skyrocketed by 91,500% over the 10-year period ending in 2019.2 In statement released with the letter, COA said these fees are “unpredictable, nonnegotiable, and often ‘clawed back’ from pharmacy reimbursement months after prescriptions are dispensed.”

COA asserts that DIR fees are tied to “irrelevant quality criteria” and cannot be contested. The effect on pharmacies and patients has been devastating, the group said. Because of claw back provisions, pharmacies have no idea what these fees will be, and the pharmacy could end up being paid less than a drug’s original cost.

"In some cases, pharmacies have been forced to close, most acutely jeop-ardizing patients in rural and underserved areas who are then forced to travel significant distances to get their medication,” COA states.

Kashyap Patel, MD, who is COA president and CEO of the Carolina Blood and Cancer Care Associates in Rock Hill, South Carolina, said patients ultimately pay the price because the fees drive up the cost of cancer treatment. “Ever since PBM behemoths have started to quietly take over the American health care system, cancer care has become more and more expensive, not less,” said Patel, who is also associate editor of Evidence-Based Oncology™.

COA’s 61-page letter raised concerns about multiple areas of the proposed rule: leaders urged CMS to exercise its authority to ensure that PBM amounts paid to pharmacies are “reasonable and relevant.”

At its annual meeting held March 16-18, COA leaders warned of the threat PBMs pose to in-house pharmacies at oncology practices. The ability to dispense drugs directly to patients is vital, the group states, because more and more oral drugs are being used in cancer care. This was especially true during the COVID-19 pandemic, when use of oral medications was preferred in some cases to prevent spread of infection.

REFERENCES
can provide your patients with access support throughout their treatment journey - we are here to help.

To learn more about the program, visit viatrisadvocate.com
FDA Approves Third Filgrastim Biosimilar: Releuko

**RELEUKO, A FILGRASTIM BIOSIMILAR** developed by Kashiv BioSciences LLC and Amneal Pharmaceuticals, Inc., is the third filgrastim biosimilar to be granted approval from the FDA. The product is also the first biosimilar to receive approval in 2022 and the first to receive FDA approval for both the Kashiv and Amneal teams.

Releuko, which references Neupogen, is indicated for the treatment and prevention of febrile neutropenia, a common chemotherapy complication among patients with cancer. The companies said they expect to launch the product during the third quarter of 2022.

“The US approval of our first biosimilar is a very significant milestone for Amneal. Biosimilars represent the next wave of providing access to affordable medicines in the United States,” Chiirag and Chintu Patel, co-chief executive officers of Amneal, said in a statement. “We are building a global biosimilars business by leveraging partner assets to start, then leveraging our own key capabilities over time.”

The companies are also working together to develop 2 other oncology biosimilars: a pegfilgrastim biosimilar, referencing Neulasta; and a bevacizumab biosimilar, referencing Avastin. Both are under review by FDA, and their launches are anticipated in 2022.

“It is a proud moment for the Kashiv team and our partners at Amneal to have our first biosimilar, Releuko, approved by the FDA,” said Chandramauli Rawal, MBBS, chief operating officer of Kashiv, in a statement. “Kashiv is one of a few domestic companies to manufacture and launch a biosimilar in the United States. Kashiv aims to continue bringing high-quality biosimilars to the global markets over the coming years.”

Releuko was approved for administration for intravenous and subcutaneous use, either as single-dose vials or prefilled syringes, both of which come in a 300-mcg/mL dose and 480-mcg/1.6 mL dose.

**References**


FDA Approves Cilta-cel to Treat R/R Multiple Myeloma

The FDA has approved Cilta-cel (cilta-cel), a B-cell maturation antigen–directed chimeric antigen receptor (CAR) T cell therapy, for the treatment of relapsed or refractory multiple myeloma. This approval is based on the CARTITUDE-1 study, which demonstrated a high response rate and durable response in patients with relapsed or refractory multiple myeloma.

The CAR-T cell therapy, developed by Janssen Biotech, is the first CAR-T cell therapy approved for the treatment of multiple myeloma, a blood cancer that affects white blood cells in the bone marrow. The approval is significant as it expands the therapeutic options available for patients with this disease.

Key Points:
- **Approval**: FDA grants approval for Cilta-cel, a CAR-T cell therapy directed against the B-cell maturation antigen.
- **Patient Population**: Approved for relapsed or refractory multiple myeloma.
- **Efficacy**: High response rate and durable response observed in clinical trials.
- **Therapeutic Potential**: Offers a new treatment option for patients with a disease that is currently incurable.

### REFERENCES


FDA Grants Breakthrough Device Designation to Foundation Medicine's ctDNA Tracker

The FDA has granted Breakthrough Device Designation to Foundation Medicine's ctDNA Tracker. This designation is intended to expedite the development and review of the device, which is designed to detect molecular residual disease (MRD) in patients with early-stage cancer.

Key Points:
- **Designation**: Breakthrough Device Designation granted to ctDNA Tracker.
- **Purpose**: To facilitate the development and review of the device for early-stage cancer.
- **Therapeutic Impact**: Could potentially lead to earlier detection and treatment of cancer.

### REFERENCES


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**FDA Approves Cilta-cel to Treat R/R Multiple Myeloma**

**THE LIST OF APPROVED** chimeric antigen receptor T-cell therapies grew on February 28, 2022, as the Janssen Pharmaceutical Companies of Johnson and Johnson and Legend Biotech’s cilta-cel received approval for treatment of relapsed or refractory multiple myeloma. The B-cell maturation antigen–directed immunotherapy will be the second such therapy for multiple myeloma, following the approval of idecabtagene vicleucel (ide-cel; Abecma) nearly a year ago. However, ide-cel, sold by Bristol Myers Squibb, has been beset by manufacturing problems since its launch, leaving room for competition.

Multiple myeloma is a cancer that affects white blood cells in the bone marrow. Although many therapies have been developed to treat it, the disease is incurable. The likelihood of disease progression rises once patients have received treatments from the 3 major therapy classes: immunomodulatory agents, proteasome inhibitors, and anti-CD38 monoclonal antibodies. Under the FDA approval, patients must receive at least 4 treatments, including 1 in each of these classes, before being considered for cilta-cel.

FDA approval is based on CARTITUDE-1 (NCT03548207), a phase 1b/2 trial in which investigators reported cilta-cel produced an objective response rate of 96% (95% CI, 92.7%–99.7%) and a stringent complete response rate of 78% (95% CI, 68.8%–86.1%). Median duration of response was 21.8 months after a median of 18 months of follow-up. Data presented at the 2021 American Society of Hematology Annual Meeting and Exposition found that 74% of patients were alive at 2 years, with progression free survival at 61%.

“The responses in the CARTITUDE-1 study showed durability over time and resulted in the majority of heavily pretreated patients achieving deep responses after 18-month follow-up,” principal study investigator Sundar Jagannath, MBBS, director of the Center of Excellence for Multiple Myeloma and professor of medicine, hematology, and medical oncology at The Tisch Cancer Institute at Mount Sinai in New York, New York, said in a statement. “The approval of cilta-cel provides physicians an immunotherapy treatment option that offers patients an opportunity to be free from antimyeloma therapies for a period of time.”

Janssen officials said in their statement that cilta-cel will be offered in a limited network at first to allow for the proper training and certification of oncologists who will administer the personalized therapy. Availability of the treatment will increase throughout 2022 and beyond, the statement said.

“This approval of Janssen’s first cell therapy is a testament to our continuing commitment in oncology to deliver new therapeutic options and drive toward our vision of the elimination of cancer,” said Mathai Mammen, MD, PhD, executive vice president of pharmaceuticals at Janssen Research and Development, LLC, Johnson and Johnson. “Today’s approval underscores our determination to develop therapies that can help patients living with what remains an intractable blood cancer today and, at the same time, offer hope for the future.”

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**FDA Grants Breakthrough Device Designation to Foundation Medicine’s ctDNA Tracker**

ON FEBRUARY 15, 2022, the FDA granted a breakthrough device designation for the Foundation Medicine, Inc circulating tumor DNA (ctDNA) detection and molecular monitoring assay, the FoundationOne ctDNA Tracker. The assay is designed to optimize algorithms for the purpose of identifying patient-specific variants and allow for the detection of ctDNA in plasma cells, according to a company statement.

The designation was given to Foundation Medicine for the assay’s ability to detect molecular residual disease (MRD) in patients with early-stage cancer after receiving curative therapy. The detection of MRD can help guide providers in making decisions on therapeutic regimens dependent on the patient’s MRD status and risk of relapse.

The assay was developed in partnership with Natera, Inc and combines Foundation Medicine’s tissue-based comprehensive genomic profiling (CGP) platform with Natera’s personalized ctDNA monitoring experience. The FoundationOne Tracker was launched by the companies in June 2021. Foundation Medicine and Natera will continue to collaborate to support biopharma and their academic partners with clinical trial evaluations and planning for companion diagnostics.

In addition to the breakthrough device designation, the assay’s personalized technology will be used for the detection of ctDNA and molecular monitoring in patients with early- or advanced-stage cancers, as well as the assessment of patient therapeutic responses, MRD detection, MRD surveillance, and detection of molecular residual relapse following curative intent therapy.

“Foundation Medicine continues to shape the future of clinical care and research by helping oncologists and our industry partners find the answers they need to bring precision cancer care to patients,” said Brian Alexander, MD, MPH, CEO of Foundation Medicine. “Personalized molecular disease monitoring enables early detection of ctDNA and can monitor for risk of relapse and track therapy response to help oncologists make personalized treatment plans for their patients. We are enthusiastic about our work to accelerate development of this assay so it can more quickly impact care decisions in the clinic.”

The FDA’s breakthrough device program is a voluntary initiative for medical devices and device-led combination products that enables more effective treatment or diagnosis of diseases or conditions that are considered life-threatening or irreversibly debilitating. The goal of the program is to accelerate the development, assessment, and review of devices while continuing to preserve the statutory standard for premarket approval and regulatory authorization. This ensures more patients and providers have timely access to the medical devices.

Data presented at the 2022 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium demonstrated the feasibility of MRD in patients with metastatic colorectal cancer who have received curative intent surgical resection. Foundation Medicine presented additional MRD data on the genomics of resected early-stage bladder cancer at the 2022 ASCO.
FDA Accepts sNDA for Zanubrutinib to Treat CLL/SLL

**THE FDA HAS ACCEPTED** a supplemental new drug application for zanubrutinib (Brukinsa; Beigene) for the treatment of adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma. The target date is October 22, 2022.1

The filing includes data from 2 pivotal randomized phase 3 studies: ALPINE (NCT03734016), comparing zanubrutinib to ibrutinib in patients with relapsed or refractory (R/R) disease; and SEQUOIA (NCT03336333), comparing zanubrutinib to bendamustine and rituximab (BR) in treatment-naïve patients. The filing also included data from 8 supportive studies in B-cell malignancies.

Zanubrutinib is already approved by the FDA for the treatment of adults with R/R marginal zone lymphoma (MZL)2 who have received at least 1 anti-CD20–based regimen, for adults with Waldenström macroglobulinemia (WM), and for adults with mantle cell lymphoma who have received at least 1 prior therapy.3

ALPINE and SEQUOIA were global studies, with patients from 17 countries. The results of ALPINE were reported at the 26th European Hematology Association (EHA21) Congress, and results from SEQUOIA were reported at the 63rd American Society of Hematology (ASH) Annual Meeting and Exposition. With superiority in investigator-assessed [objective response rate] over ibrutinib in ALPINE for relapsed or refractory patients and in PFS [progression-free survival] over chemoimmunotherapy in the SEQUOIA study for treatment-naïve patients, Brukinsa has demonstrated its potential to improve treatment outcomes for CLL patients,”1 Jane Huang, MD, chief medical officer of hematology at Beigene, said in a statement.2

Zanubrutinib is a next-generation Bruton tyrosine kinase (BTK) inhibitor that minimizes the off-target inhibition of TEC- and EGF-family kinases seen with ibrutinib, which has been the standard of care in CLL. This more targeted treatment improves outcomes and reduces toxicity, Peter Hilman, PhD, MB, CHI, professor at the University of Leeds and honorary consultant hematologist at Leeds Teaching Hospitals NHS Trust in the United Kingdom, explained while presenting interim results of ALPINE at EHA21.2

SEQUOIA found zanubrutinib produced prolonged PFS compared with BR. The estimated 24-month PFS was 85.5% for zanubrutinib vs 69.5% for BR. The estimated overall survival was 94.3% vs 94.6%.2

Constantine S. Tam, MD, MBBS, a consulting hematologist and professor at Peter MacCallum Cancer Centre in Melbourne, Australia, and lead author on a SEQUOIA abstract, presented at ASH 2021, noting that zanubrutinib had better tolerance with reduced adverse events compared with the BR arm. “This confirms the highly tolerable nature of BTK inhibitors in general,” he said in an interview with *The American Journal of Managed Care*.4

In addition, although BTK inhibitors are associated with atrial fibrillation, in SEQUOIA, the rates of atrial fibrillation were the same as the comparator arm. “This confirms earlier data that [demonstrated] zanubrutinib is less cardiotoxic than other BTK inhibitors, and in particular, less cardiotoxic than ibrutinib,” Tam said.4

Jennifer R. Brown, MD, PhD, director of the CLL Center at Dana-Farber Cancer Institute in Boston, Massachusetts, and principal investigator of ALPINE and SEQUOIA, echoed in a statement the safety and efficacy benefits of zanubrutinib. “[Although] previously approved BTK inhibitors have been transformational for some patients with CLL, there continues to be unmet need, as not all patients achieve a favorable clinical response, [whereas] others are unable to tolerate currently approved BTK [inhibitor] therapies,” she said. “As demonstrated in both the ALPINE and SEQUOIA studies, Brukinsa was generally well tolerated in CLL patients, with low rates of atrial fibrillation, and showed strong efficacy compared [with] ibrutinib and chemoimmunotherapy, respectively.”

The European Medicines Agency also accepted applications for zanubrutinib in CLL and MZL. The therapy is currently approved for patients with WM who have received at least 1 prior therapy or for first-line treatment of patients unsuitable for chemoimmunotherapy.1

**REFERENCES**


**MANAGED CARE UPDATES**

**Further Analysis Needed to Incorporate Liquid Biopsy in Community Setting**

**POTENTIAL BENEFITS OF INCORPORATING liquid biopsy into community-based oncology practices include early signal-based therapeutic matching, referral to appropriate signal-based clinical trials, and improved survival outcomes, according to retrospective study findings published in The Oncologist.** This study was conducted using charts from 178 patients receiving care for advanced solid malignancies at Cancer Center of Wichita, Kansas, and a liquid-based assay was used to evaluate these malignancies between December 2018 and December 2019. Liquid biopsy has a favorable utility profile in
that it is less invasive vs tissue-based biopsy, and next-generation sequencing of circulating tumor DNA has higher sensitivity, they highlighted.

There was a follow-up at 1 year to evaluate treatment assignment and survival. Study end points included progression-free survival (PFS) in cases of lung, breast, and colorectal cancer and overall survival (OS) in patients with lung, breast, and colorectal cancer.

“Liquid biopsy testing offers a significant potential in selecting signal-matched therapies for advanced solid malignancies,” the authors wrote. “The feasibility of liquid biopsy testing in a community-based oncology practice, and its impact on selecting signal-matched therapies, and subsequent survival effects have not previously been reported.”

Among the 178 patients tested, 98% tested had a new diagnosis, advanced cancer, or recurrent disease with not enough tissue for testing. The remaining 2% were tested following first-line treatment failure. Most patients also had stage IIIIB disease and above, the mean age at diagnosis was 65 years, and the most common cancers were lung (50.56%), breast (17.42%), and colon (7.87%). Seventy-nine percent of the study cohort (n = 140) tested positive for mutations, with these individuals subdivided into patients with actionable mutations with an FDA-approved targeted treatment (n = 32), actionable mutations with an FDA approval used off-label (n = 73), and unactionable mutations (n = 35).

Overall, 481 genetic alterations were identified, with the mean per liquid biopsy being 3.1 (2.14). The highest average per test were seen among colon cancer (4.36), breast cancer (2.97), prostate cancer (2.73), and lung cancer (2.59). The 3 cancers with the most detected somatic mutations overall were lung, breast, and colon, respectively. Of the 481 total alterations, 95% were actionable. Within this group, the most common altered genes were TP53 (32.17%), PIK3CA (8.53%), EGFR (7.66%), and KRAS (7.22%).

Ninety-five percent of those who tested positive for mutations were candidates for targeted treatment (n = 135), with most receiving an unmatched therapy. Further, for those designated candidates for FDA-approved treatments, only half received a targeted treatment, close to 7% received a treatment off-label, and 10% were referred to signal-based clinical trials. The most common reason for not receiving a signal-matched treatment among participants with 1 or more actionable mutations was treatment availability.

Following a subanalysis of survival rates at 1 year seen among patients with lung, breast, or colon cancer who received a matched therapy following liquid biopsy and those who did not, the following results were seen:

- The matched group had more patients with breast cancer vs the unmatched group: 27.3% vs 15.9%
- Fewer patients with lung cancer and colorectal cancer were seen in the matched vs unmatched group: 63.6% vs 72.7% and 9.1% vs 11.4%, respectively
- Median overall survival (mOS) was 13 (range, 11.4-14.6) months
- The matched vs the unmatched cohort had a longer mOS (15 vs 13 months) and PFS (12 vs 5 months)
- Statistically significant differences were not seen in either OS or PFS among the patients who received matched treatment and had higher or lower matching scores (ie, the higher the score, the better the treatment match, according to the authors)

The study authors highlight that their findings are important because their patients were tested up front for alterations, prior to treatment, vs having already undergone several lines of treatment, and the results echo previous research. In addition, their data bear out that combining matched therapies for use in patients with several actionable mutations is a potential treatment pathway. “Other studies have also suggested that treatment with single-agent matched therapy resulted in significantly lower response rates compared with combination therapy,” the authors wrote.

Still, large prospective controlled clinical trials are needed to confirm their findings and to investigate whether providing community-based liquid biopsy testing facilitates betterment of quality of life, early cancer detection, disease monitoring, and cost benefits compared with tissue-based biopsy.

**REFERENCE**


**Study on Types of Pain in MM Reveals Communication Inadequacies Between Physicians, Patients**

**IN ADDITION TO EXPERIENCING** bone pain, patients with multiple myeloma (MM) were found to experience multiple types of pain, including significant physical, social, and emotional pain, signaling that there is a disconnect between health care providers and patients in how pain symptoms and severity are reported and managed. The study findings, which were published in *Pain Management*, found discordance in the communication between patients and physicians, leading to many physicians underestimating or underreporting pain symptoms and severity among their patients, showing that improved pain communication between parties is needed.

“Simply relying on the physical aspect of pain may not adequately reflect the true severity and impact of pain in clinical practice. Our findings suggest that a comprehensive assessment of pain must consider not [only] physical symptoms but also other dimensions, including social and emotional factors, relating to burden of disease and quality of life.”

—study authors

“Strategies to reduce the burden of bone pain, including patient education surrounding bone health, lifestyle changes, physical activities as prevention techniques, and supplements and medications to support bone health and prevent bone complications, should also be implemented, as well as optimizing professional qualification of the treatment physician,” the investigators wrote.

Despite knowing pain management is integral to cancer care and that patients with MM experience a high-symptom burden, undertreatment of pain is common. Some of the reasons that patients’ pain goes undertreated can include patients and physicians lacking knowledge or understanding about pain, a physician may fail to understand the impact of pain on patients with cancer, and potential poor communication between physicians and patients. Additionally, a patient may be reluctant to admit they are in pain, and there is a lack of published studies on the different aspects of pain that affect people with cancer.

Between November 20, 2017, and February 1, 2018, the investigators collected data from the Adelphi Multiple Myeloma Disease-Specific Programme patient-level database, which contained information from surveys that were conducted during routine in-person appointments in Germany and Italy. For eligibility, patients had to be 18 years or older, have symptomatic MM, and have received either first-line or second-line MM therapy. A detailed questionnaire was completed by a treating physician for each patient.

In total, 330 patients were included, 62.7% of whom were women and 65.5% were retired. The mean age of the cohort was 68 years. The median time since
Receiving an MM diagnosis was 0.97 years. Overall, 277 had clinically important physical pain, with 73 reporting no physical pain, 161 reporting mild pain, 81 experiencing moderate pain, and 15 patients having severe pain. Most of the cohort (87.6%) said they had experienced bone pain during the 7 days prior to the survey.

The investigators said there was a low level of agreement between patient and physician responses regarding bone pain and bone pain symptoms. Approximately half of physicians were found to have underestimated the severity of bone pain that their patients experienced, and not all patients who experienced bone pain had their symptoms recorded by a physician.

Of the 327 patients who responded about emotional pain, 58% said they experienced clinically important emotional pain. Among the 329 patients who gave responses about social pain, 74 reported clinically important social pain. Emotional and social pain became progressively worse with increasing MM severity.

"Simply relying on the physical aspect of pain may not adequately reflect the true severity and impact of pain in clinical practice. Our findings suggest that a comprehensive assessment of pain must consider not only physical symptoms but also other dimensions, including social and emotional factors, relating to burden of disease and quality of life," the investigators said. The investigators also suggested physicians adopt a more holistic approach to pain identification and management, where providers ask open-ended questions to consider all aspects of pain to reduce symptoms and improve quality of life.

The study had some limitations, including that the proportion of patients with severe pain was small. Additionally, collecting data during consultations prevented the authors from making conclusions on causal relationships. "As health care evolves and patient-physician consultations shift from face-to-face clinics to virtual consultations, it is even more important that communication on pain and symptom burdens of disease are effective, and the patient voice is captured accurately," the investigators said. 

REFERENCE

Possibility of Breast Cancer Overdiagnosis Should Inform Mammography Decisions

ALTHOUGH THEIR FINDINGS of breast cancer overdiagnosis from annual or biennial mammography were not as high as previous studies, the authors of a new study published online in Annals of Internal Medicine caution their findings also indicate need for increased collaborative decision-making on this screening method.

For their study, they defined overdiagnosis as, "mammographic detection of cancer that would not become clinically relevant in the woman’s remaining lifetime." They also placed blame on variations in overdiagnosis definitions, study settings, and estimation methods for the 0% to 54% estimate in overdiagnosis range found.

"Knowledge about overdiagnosis is critical for supporting shared decision-making, as recommended by the United States Preventive Services Task Force and the American Cancer Society," they wrote. "However, the risk for breast cancer overdiagnosis in contemporary screening programs remains uncertain."

Their data on 35,986 women of ages 50 to 74 years (12.1% Black, 19.0% Asian, and 64.4% White), who underwent 1 or more screening mammograms from 2000 to 2018 at a Breast Cancer Surveillance Consortium (BCSC) facility, showed 82,677 total mammograms (mean, 2.3 [range, 1-17]) and a 0.87% breast cancer diagnosis rate (n = 718 cancer diagnoses; 79.0% invasive; 21.0% in situ). For those cases determined to be preclinical cancers (those that have not produced symptoms or signs of cancer), 4.5% (95% CI, 0.1%-14.8%) were nonprogressive.

The authors note that their findings on overdiagnosis are both higher than previous modeling studies because of differences in screening practices, diagnostic practices, and modeling assumptions, and lower than excess-incident studies because they are "prone to overestimation."

An accompanying editorial noted the ongoing controversy surrounding breast cancer overdiagnosis and proposed several solutions, including the following:

• Prediction models must be more accurate to influence treatment decisions
• Screening technologies must improve to reduce the risks of overdiagnosis and missing breast cancer already missed by mammography
• Screening mammograms could be more effective if they are part of individualized (by risks and preferences) multipronged strategies for cancer risk reduction

Still, the authors of the present study believe their results are strong because of the several sensitivity analyses they conducted. Their Bayesian modeling approach showed lack of influence on their predictions from model structure and prior distribution variations and accounted for parameter uncertainty, respectively. Because of this, they hope their findings will contribute to a more informed mammography screening process.

“We hope our findings will bring the field closer to a consensus estimate and facilitate decision-making about mammography screening,” they said. “Our estimates of the frequency and age dependence of overdiagnosis can be provided along with information about false-positive rates to balance estimates of mammography screening benefits as part of a process of shared and informed decision-making.”

REFERENCE
Study Evaluates Impact of AE Severity on Health State Utility for CAR T Treatment in LBCL

WITH MULTIPLE CHIMERIC ANTIGEN RECEPTOR (CAR) T-cell therapies available, understanding the health state utilities associated with toxicities of treatment can provide a way to compare the value of these treatments. As may be expected, more severe adverse events (AEs) are associated with greater disutility, or utility decrease, in large B-cell lymphoma (LBCL), according to a study published in *PharmacoEconomics – Open*.

Two important toxicities associated with CAR T-cell therapies are cytokine release syndrome (CRS) and neurological events (NEs). Both can become severe and require intensive treatments. Rates of severe CRS have ranged from 2% to 22% in clinical trials for various CAR T-cell therapies, and rates of NEs have ranged from 10% to 28%.

“As more CAR T-cell treatments are introduced, cost-utility analyses (CUAs) can be used to examine their value and inform decision-making on health care resource allocation,” the authors said. Health state utilities, which are valued to 0 (dead) and 1 (full health), are factored into CUAs to calculate quality-adjusted life-years. “Because the CAR T-cell therapies differ in the rates of CRS and NEs, a CUA comparing these treatments should incorporate utility differences associated with these [AEs],” the authors wrote. These are life-threatening events that require intensive treatments, such as mechanical ventilation.

The clinician reports of the typical patient experience of each AE and the published literature of AE reports from a clinical trial were used to maximize the representativeness of these health state vignettes. A pilot study tested the time trade-off methods with a sample of the general population. The EQ-5D-5L, which comprises 5 dimensions to describe and value health, was administered to characterize the health status of the sample population.

A total of 366 potential participants were reached but only 218 interviews were included in the analysis, with 113 patients from London and 105 patients from Edinburgh. Although age, sex, marital status, and education level were similar between the 2 groups, the Edinburgh group had a higher rate of White patients and a lower rate of patients employed full time.

Depression, anxiety, diabetes, arthritis, and hypertension were the most common medical and mental health conditions, but 43.6% reported no health conditions. None of the participants reported having a diagnosis of LBCL, but 9 said they knew someone with LBCL. Another 5 participants were diagnosed with another type of lymphoma, and 57 knew someone with another type of lymphoma. The results of the EQ-5D-5L found few issues with mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

In the study, the participants ranked the health states in order of preference, with health state A (no AEs) ranked as most preferable by all participants, health state D (grade 3/4 CRS), and health state F (grade 3/4 NE) ranked as least preferable. Mean utility scores ranked from most preferred to least were A (0.73), B (0.71), C (0.69), D (0.68), E (0.67), and F (0.55). Mean rankings from most preferred to least were A (0.73), B (0.71), C (0.70), D (0.68), E (0.67), and F (0.55). "Most participants perceived all health states as better than dead,” they noted. The Edinburgh group has consistently lower utility scores for health states B through F, but there was no significant difference in the utility for health state A.

The limitation of this kind of study is that the scores represent the general population and not the experience of the actual patients. “The rates and severity of the AEs represented in the health states can differ across the CAR T-cell treatments. By incorporating disutility of these AEs, CUAs can more accurately and comprehensively model the differences among available treatments for LBCL,” the authors said.

**REFERENCE**


**CLINICAL UPDATES**

Tumor Mutational Burden May Help Predict Immunotherapy Response in Metastatic NSCLC

**TUMOR MUTATIONAL BURDEN** (TMB) was associated with immunotherapy response and survival outcomes in patients with metastatic non–small cell lung cancer (NSCLC), according to study findings published in *Oncotarget*. Although immune checkpoint inhibitors have substantially improved clinical outcomes for some patients with metastatic NSCLC, determining which patients would most benefit from the drugs has generated inconsistent findings for biomarkers such as PD-L1.

“Improved patient selection would better identify patients who benefit from immunotherapy as well as spare patients predicted as nonresponders from needless toxicity and cost,” noted investigators.

TMB measured by comprehensive genomic profiling (CGP) has emerged as a potential biomarker to predict a tumor’s sensitivity to immuno-oncology agents in a variety of advanced cancers. Moreover, high TMB has consistently been associated with improved clinical benefit among patients receiving immunotherapy for NSCLC, said the study authors.

The investigators sought to further assess the association of TMB with treatment response and survival outcomes in patients with metastatic NSCLC. They conducted a real-world multisite study to evaluate clinical outcomes by TMB collected from tissue samples among patients with stage IV NSCLC between 2012 and 2019 who were treated with immunotherapy-containing regimens in the first-line setting and underwent CGP.

In the study, 667 patients with NSCLC at 9 US cancer centers were stratified by initial TMB mutations/megabase (mut/Mb) measures of greater than or equal to 10 mut/Mb (high; n = 272) and less than 10 mut/Mb (low; n = 395).

“The majority of patients received CGP from Foundation Medicine (64%), followed by Caris (20%), and OncoPlex (8%). Foundation Medicine was widely »

"Grade 3/4 AEs (described in health states D and F) had substantially larger disutilities than the less–severe AEs (described in health states B, C, and E),” the authors wrote. These are life-threatening events that require longer hospitalization and possibly intensive treatments, such as mechanical ventilation.

Participants were most willing to trade time in perfect health to avoid living in health state D (89.0%), followed by F (86.7%), C, E (78.9%), B (75.2%), and A (72.0%). “Most participants perceived all health states as better than dead,” they noted. The Edinburgh group has consistently lower utility scores for health states B through F, but there was no significant difference in the utility for health state A.

The limitation of this kind of study is that the scores represent the general population and not the experience of the actual patients. “The rates and severity of the AEs represented in the health states can differ across the CAR T-cell treatments. By incorporating disutility of these AEs, CUAs can more accurately and comprehensively model the differences among available treatments for LBCL,” the authors said.

**REFERENCE**

Natural Killer Cell–Based Immunotherapy: A Less Toxic Treatment for Leukemia?

ALTHOUGH CHEMOTHERAPY AND RADIATION have long been standard treatments for leukemia, immunotherapies have been increasingly researched and are considered promising options. A recent review assessed current research on natural killer (NK) cells, which serve as the first line of defense against cancer and play a key role in mitigating abnormal cell population growth. The review, published in *Cancers*, also explores the cells’ potential use in leukemia treatment. Authors are from the University of North Texas Health Science Center in Forth Worth and Baylor Scott and White Sports Therapy and Research at The STAR, Frisco, Texas.

Leukemia is a bone marrow and blood cancer characterized by irregular hematopoietic stem cell differentiation, with main subtypes including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL). NK cells play a key role in the recognition and cytolysis of abnormal and rapidly proliferating cell populations.

Traditional chemotherapy and radiation cause nonspecific cell destruction and increase patients’ susceptibility to infection, adverse effects, and immune cell inactivation. However, immunotherapies such as NK cell–based therapy are targeted and antigen specific, using the patient’s own immune system to fight cancer cell growth.

NK cells typically make up approximately 10% of lymphocytes circulating in the body, moving in a latent state until receptor-ligand interactions stimulate them. NK cells do not have cytotoxic properties when in contact with healthy host tissues or cells, but they release lytic granules or produce cytokine to destroy any virally infected or cancerous cells they encounter. Research has shown that leukemia results in a decrease in the number of active NK cells as well as in their cytotoxic and degranulation abilities.

Thus, NK cell–based immunotherapy aims to increase NK cell activation by blocking the inhibitory interactions that occur when these cells encounter healthy cells under normal conditions. This type of treatment also expands NK cell populations and enhances their overall function. NK cell–based immunotherapies being studied for leukemia treatment include the following:

- adoptive transfer
- monoclonal antibodies (mAbs)
- chimeric antigen receptor–NK cells (CAR-NKs)
- bispecific/trispecific killer engagers (BiKEs/TriKEs)

Current research on these therapies aims to induce complete remission in patients and minimize the adverse effects often associated with them.

**MONOCLONAL ANTIBODIES.** One of the most common forms of NK cell–based therapy are mAbs, which block specific biomarkers and increase antibody-dependent cellular cytotoxicity to boost NK cell function. Combination therapy with different types of cytokines is one potential method of increasing NK cell populations. A small phase 1 trial of NK cells combined with the mAb rituximab after chemotherapy produced a complete response in 7 of 9 patients.

**ADAPTIVE TRANSFER.** This method involves isolating NK cells from the peripheral blood, bone marrow, or umbilical cord of the patient (autologous) or a healthy donor (allogeneic) and purifying or genetically modifying the cells with cytokines before infusing them back into the patient. When the NK cells encounter incompatible ligands, graft-versus-leukemia can occur and increase their activity, killing leukemic cells. This has proved effective in AML especially, although relapse is common and posttransplant pharmacological intervention is a key aspect of success.

**CAR-NK CELL THERAPY.** This treatment is in experimental phases, but it may be capable of killing cancer with minimal risk of toxicity or graft-vs-host disease (GVHD). This makes CAR-NK a potentially less toxic option than CAR T-cell therapies, which have shown success in refractory and relapsed B-cell ALL cancers but often cause neurotoxicity or cytokine release syndrome (CRS) and come with a higher risk of GVHD. CAR-NK also has the potential to be more accessible because it does not have to be individualized to each patient and can come in an off-the-shelf form.

**BIKES AND TRIKES.** These are engineered mAbs, created by fusing together single-chain variable fragments to make them bi- and trispecific for certain tumor antigens. NK cells can recognize the BiKEs or TriKEs, then induce apoptosis of their target. The study authors note that whereas BiKEs have shown some success in inducing antibody-dependent cellular cytotoxicity on target cells, TriKEs have shown superiority in inducing cytotoxicity, degranulation, and cytokine production.

Leukemia cells have been shown to be capable of manipulating expression of NK cell receptors to go unrecognized by NK cells, and targeting the biomarkers involved in this process could also be an avenue of treatment as these therapies are explored. Specifically, NK cell receptors 2B4, C5, and LLT1 may be effective targets.

Continued research and more clinical trials are needed to determine the effectiveness of NK cell–based treatments, although there are some ongoing trials. Researching the specific receptor-ligand interactions that make NK cells cytotoxic in the presence of cancer cells may also aid in the understanding of these treatments, the authors noted.

Overall, the review authors see great potential in NK cells as future leukemia treatments are developed. “In addition to providing an alternative therapy for patients who may not respond to conventional treatment, NK cell immunotherapy focuses on harnessing a patient’s own immune system to fight cancer proliferation, minimizing off-target effects,” they wrote.

**REFERENCE**

First- and second-generation EGFR TKIs have limited efficacy in patients with EGFR Exon20 insertion+ mNSCLC

Overall survival for EGFR Exon20 patients is half that of patients with common EGFR mutations when treated with first- and second-generation EGFR TKIs*.

Overall response rates when treated with first- and second-generation EGFR TKIs.<

PCR testing identifies only 50% of EGFR Exon20 insertions. NGS is able to detect all EGFR Exon20 variants.1-9

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*These results were not statistically significant (P=0.06).1*  
EGFR, epidermal growth factor receptor; mNSCLC, metastatic non-small cell lung cancer; NGS, next-generation sequencing; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor.

Considerations to Increase Rates of Breast Cancer Screening Across Populations

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Abstract

OBJECTIVES: COVID-19 has caused considerable drops in utilization of breast cancer screening services during the pandemic, especially among certain racial and ethnic groups. Members of the Community Oncology Alliance (COA)—including the COA president, South Carolina oncologist Kashyap Patel, MD—have reported increases in patients, particularly those of color, presenting with stage III and IV cancer at diagnosis. According to data released by the Biden administration, more than 9.5 million recommended cancer screenings had been missed in the United States as a result of the COVID-19 pandemic, as of February 2022. President Joe Biden and First Lady Jill Biden, EdD, aim to address this in the 2022 Preventive Services Task Force breast cancer screening guidelines, devoting considerable attention to reassessing how health equity and social determinants of health (SDOH) contribute to discrepancies in breast cancer screening, diagnosis, treatment, and outcomes. The impact of the COVID-19 pandemic on utilization of breast cancer screenings and subsequent advanced-stage diagnoses for many patients highlights the need for revised breast cancer screening recommendations. Although a report from a Massachusetts health system review of 192,060 patients undergoing cancer screening found that cancer screenings returned to nearly prepandemic levels between June and September 2020, we sought to examine a multipayer data set to determine if the recovery in breast cancer screenings was felt evenly across ethnic and racial subgroups and if there were any differences in recovery rates based on insurance status. According to analyses from the US Census Bureau, beneficiaries with commercial health insurance are more likely to have higher incomes than those enrolled in Medicare fee-for-service (FFS) or managed Medicaid.

METHODS: Using a multipayer database, we analyzed breast cancer screening rates for 2 periods—March 1 to September 30, 2019, and March 1 to September 30, 2020—among Medicare fee-for-service (FFS), managed Medicaid, and commercial insurance beneficiaries to understand the potential impact of the COVID-19 pandemic on adherence to the US Preventive Services Task Force breast cancer screening recommendations, which are currently under review. Screening rates were evaluated across 5 racial/ethnic groups and by payer type.

RESULTS: Mean monthly mammogram screening rates among eligible White Medicare FFS beneficiaries dropped to 0.6% in April 2020, but these screening rates recovered to 6.5% by June 2020. Screening rates for eligible Black Medicare FFS beneficiaries recovered on a pace slightly slower than that of White beneficiaries, but more rapidly than that of other groups. By comparison, American Indian/Alaska Native beneficiaries had a mean monthly screening rate of 0.5% in April 2020, which recovered to 3.1% in June 2020; these were below 2019 screening rates of 4.2% for April and 3.9% for June. Differences in screening rates by payer type were also observed. Patients with commercial insurance had higher screening rates compared with those covered by Medicare FFS and managed Medicaid.

CONCLUSIONS: Our principal finding shows that mean breast cancer screening rates decreased in April 2020 across all payers, but recovery to prepandemic screening levels has occurred more slowly among certain racial and ethnic minority groups. Differences in recovery rates by payer type highlight a strong relationship between income level and screening utilization.

USPSTF recommendations play a significant role in ensuring coverage for preventive services, such as cancer screenings. Under federal law, all private payers and Medicare are required to cover services that are given ‘A’ or ‘B’ recommendations from the USPSTF. The only exception is the Medicaid market, where there is variability from state to state in how preventive services are covered. Study results have highlighted the effect of the March 2020 public health emergency (PHE) in response to the COVID-19 pandemic on cancer screening rates and how the PHE widened health care disparities among racial and ethnic groups. In November 2020, we reported sharp declines in cancer care, including screenings, following the declaration of the PHE. In June 2021, data reported by the CDC showed an 87% drop in breast cancer screening rates in April 2020, compared with prepandemic rates.

Disparities in screening rates predate the pandemic. A decade ago, data published prior to passage of the Affordable Care Act found disparities in access to high-quality mammography, with Black and Hispanic women without insurance less likely to have access. In 2017, Narayan et al found that income, education level, and access to insurance were predictors of screening rates. In May 2021, USPSTF published a Final Research Plan as part of the organization’s effort to update its breast cancer screening guidelines, devoting considerable attention to reassessing how health equity and social determinants of health (SDOH) contribute to discrepancies in breast cancer screening, diagnosis, treatment, and outcomes. The impact of the COVID-19 pandemic on utilization of breast cancer screenings and subsequent advanced-stage diagnoses for many patients highlights the need for revised breast cancer screening recommendations. Although a report from a Massachusetts health system review of 192,060 patients undergoing cancer screening found that cancer screenings returned to nearly prepandemic levels between June and September 2020, we sought to examine a multipayer data set to determine if the recovery in breast cancer screenings was felt evenly across ethnic and racial subgroups and if there were any differences in recovery rate based on insurance status. According to analyses from the US Census Bureau, beneficiaries with commercial health insurance are more likely to have higher incomes than those enrolled in Medicare fee-for-service (FFS) or managed Medicaid.

Data and Methods The Community Oncology Alliance (COA) and Avalere Health conducted an evaluation to measure...
and compare adherence to USPSTF breast cancer screening guidelines prior to the COVID-19 pandemic (March 1 to September 30, 2019) and during the PHE (March 1 to September 30, 2020) across multiple payer populations and social risk factors (eg, race/ethnicity, income). The analysis utilized Inovalon’s MORE® Registry, a multipayer database that captures the enrollment and claims data of more than 338 million Medicare FFS, Medicare Advantage, managed Medicaid, and commercial beneficiaries, and Axon’s InfoBase Geo database to link and integrate patient-specific SDOH information at the 5-digit zip code level.

Results

RACIAL/ETHNIC DISPARITIES. Our results illustrate patterns of mammogram use among 5 racial/ethnic groups in the period from March 2020 to September 2020, covering the onset of the pandemic, the declaration of the PHE, and the period when screening rebounded after the initial decline. The illustrations compare this 6-month period with the corresponding period in 2019. Results are presented for 5 groups: White, Black/African American (hereafter, Black), Hispanic/Latino (hereafter, Hispanic), Asian/Native Hawaiian/Pacific Islander (hereafter, Asian), and American Indian/Alaskan Native. Data show that mammogram utilization among 3 groups (Asian, Hispanic, and American Indian/Alaskan Native) was already lower in 2019 than utilization among White beneficiaries and, moreover, dropped even more precipitately at the start of the pandemic in 2020 (Figure 1).

In like manner, Figure 1 highlights how breast cancer screening utilization recovered more rapidly in White and Black subgroups during the period immediately following declaration of the PHE and prior to the emergence of the Delta and Omicron COVID-19 variants.

Meanwhile, the analysis found that the Asian, Hispanic, and American Indian/Alaskan Native groups did not experience a rebound in screening rates until September 2020, and eligible Asian and Hispanic Medicare beneficiaries’ screening rates did not fully recover during the same period. This observation aligns with findings published in the Journal of Clinical Imaging that showed higher mammogram cancellation rates among non-White patients.13 The trend in monthly screening across race and ethnicity categories was also observed in the screening utilization patterns over a 24-month period—a critical shift as USPSTF guidelines on breast cancer screening for women aged 50 to 74 years recommends screening every 2 years.

DISPARITIES BY PAYER TYPE. Screening rate disparities were also observed across payers (Figure 2). Data on prepandemic screening rates showed that managed Medicaid beneficiaries had the lowest screening rates compared with individuals covered by commercial and Medicare FFS policies. Furthermore, Figure 2 underscores that adherence to the USPSTF 24-month breast cancer screening guidelines is consistently lower for managed Medicaid beneficiaries, demonstrating the need to better understand the downstream implications of delayed screening across these subpopulations. Indeed, USPSTF recommendations for screening do not dictate Medicaid coverage in the same way they do for commercial and Medicare FFS patients, and screening utilization in this population remains low.

Avalere’s review also identified a strong relationship between rates of screening and median household income, regardless of race and ethnicity, consistent with earlier findings.14 Specifically, screening rates increased as a function of median household income, dividing patients into approximately 3 income groups: less than $40,000; $40,000 to $75,000; and $75,000 and above. The relationship was observed in both the commercial and managed Medicaid markets, although the relationship between increased screening utilization and higher income level was more prominent in the commercial segment.15

FIGURE 1. Eligible Medicare FFS Monthly Breast Cancer Screening Mammogram Rate Across Race and Ethnicity by Month, 2019 vs 2020

FIGURE 2. Eligible 24-Month Breast Cancer Screening Rate by Payer, February 2018-January 2020

Note: As part of the statistical deidentification process of Inovalon’s MORE® Registry, the American Indian and Alaskan Native category was removed from the data set.

FFS, fee for service.

Note: The mean numbers of Medicare FFS beneficiaries from the monthly 2019-2020 analysis were 1,381,059 (White), 190,768 (Black/African American), 43,940 (Asian, Native Hawaiian, other Pacific Islander), and 11,877 (American Indian/Alaskan Native).
Discussion

Given these findings, addressing screening inequities related to race, ethnicity, and income should be a top priority for patients and providers. First and foremost, USPSTF screening recommendations provide a pathway to coverage for many preventive services without cost sharing in the commercial and Medicare markets.

In addition, current recommendations for cancer screenings do not systematically address disparities in care, namely that adherence to preventive service recommendations is lower among certain racial and ethnic minority groups, illustrating historical inequities in provision of services and outcomes that disproportionately affect minority populations.11 Timely screening is only one part of ensuring prompt diagnosis to improve equity in outcomes across subpopulations with increased social risk factors. Essential follow-up tests and procedures may not be covered by insurance, further delaying timely diagnosis and treatment of disease.

The disruption to cancer screening delivery during the COVID-19 pandemic will have a long-term impact on cancer care. Providers predict later-stage diagnoses and significantly worse outcomes.16 As the president of COA, South Carolina oncologist Kashyap Patel, MD, told The Washington Post, “COVID-19 put cancer and health care disparities on steroids.”17

USPSTF recommendations allow for coverage of preventive screening services receiving an “A” or “B” grade from the Task Force without cost sharing. Beyond USPSTF recommendations, there are a broader set of cancer prevention services that play an important role in the timely diagnosis of cancer. Coverage of these services among public and private plans, as well as value-based insurance design arrangements, is paramount in addressing delays in diagnosis, treatment, and care.

Limitations

This study had several limitations. When analyzing the impact of SDOH factors, mean screening rates were based on a patient’s 5-digit zip code. For example, trends by median household income were based on the 5-digit zip code of the patient and not the individual patient’s income. Furthermore, USPSTF screening guidelines offer minimum coverage of screening services for preventive care, compared with other breast cancer screening organization guidelines such as those of the American Cancer Society and the National Comprehensive Cancer Network. Other forms of screening and preventive services for early detection of breast cancer are cited and included in guidelines across multiple other compendia, but for the purpose of this assessment, we only reviewed screening adherence rates in comparison with USPSTF guidelines.

There were also differences in the number of beneficiaries included across insurance types (ie, Medicare FFS, commercial, and managed Medicaid) and time frames (ie, monthly profile analysis and 24-month profile analysis). For Medicare FFS, a 20% random sample of all Medicare FFS enrollees was used. For commercial and managed Medicaid beneficiaries, a convenient sample of those enrollees was used. There were limitations in insights into beneficiaries who switched payers outside of the sample used. In addition, there were limitations in race/ethnicity data; this information was sourced from payers, where either race or ethnicity is known. Information on biracial and multiracial beneficiaries is typically not known.

“Timely screening is only one part of ensuring prompt diagnosis to improve equity in outcomes across subpopulations with increased social risk factors. Essential follow-up tests and procedures may not be covered by insurance, further delaying timely diagnosis and treatment of disease.”

Conclusions

Given that the USPSTF is currently in the Final Research Plan stage of updating draft recommendations for breast cancer screening, a final recommendation statement is imminent. Access to high-value preventive services can improve the speed of cancer diagnosis as well as increase adherence to recommended follow-up procedures and treatments for these patients. A broader set of stakeholders and targeted care delivery and communications can help close these gaps in care. Notably, the Cancer Moonshot initiative intends to leverage stakeholders such as government partners, business community, and nonprofit sectors to address inequities in screening, diagnostics, and treatment across race, gender, socioeconomic status, and other SDOH risk factors. To the extent to which some of these disparities disproportionately impact breast cancer outcomes for different populations, policies that reverse these trends, to target high-risk populations for screenings and to improve broader payment and delivery innovation for cancer care, may be warranted. ◆

AUTHOR INFORMATION

For the Community Oncology Alliance (COA): Patt, of Texas Oncology, member of the executive committee; Gordon, of Florida Cancer Specialists and Research Institute, member of the board of directors; Patel, of Carolina Blood and Cancer Care Associates, president; Okon, executive director; and Forness, managing director of policy, advocacy, and communications. For Avalere Health: Markward, principal research scientist; Sullivan, principal; Burnett, manager/consultant; Gatchel, senior associate; and Harris, senior policy associate.

REFERENCES


**INDICATION**

SARCLISA (isatuximab-irfc) is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor.

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

**Infusion-Related Reactions**

Serious infusion-related reactions (IRRs), including life-threatening anaphylactic reactions, have occurred with SARCLISA treatment. Severe signs and symptoms include cardiac arrest, hypertension, hypotension, bronchospasm, dyspnea, angioedema, and swelling. Based on ICARIA-MM, IRRs occurred in 38% of patients treated with SARCLISA, pomalidomide, and dexamethasone ( Isa-Pd). All IRRs started during the first SARCLISA infusion and resolved on the same day in 98% of the cases.

In IKEMA, infusion-related reactions occurred in 46% of patients treated with SARCLISA, carfilzomib, and dexamethasone ( Isa-Kd). In the Isa-kd arm, the infusion-related reactions occurred on the 1st infusion day in 59% of episodes. In patients treated with Isa-Kd, 95% of those experiencing an infusion-related reaction experienced it during the first cycle of treatment. All infusion-related reactions resolved: within the same day in 74% of episodes, and the day after in 24% of episodes.

The most common symptoms (≥5%) of an infusion-related reaction in ICARIA-MM and IKEMA (N=329) included dyspnea, cough, nasal congestion, and nausea. Anaphylactic reactions occurred in less than 1% of patients. To decrease the risk and severity of IRRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H2 antagonists, diphenhydramine or equivalent, and dexamethasone.

Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade 2 reactions, interrupt SARCLISA infusion and provide appropriate medical management. After patients with grade 2 or grade 3 reactions, if symptoms improve to grade ≤1, restart SARCLISA infusion at half of the initial infusion rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally. In case symptoms do not improve to grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite appropriate medications, or require hospitalization, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA if an anaphylactic reaction or life-threatening (grade 4) IRR occurs and institute appropriate management.

**Neutropenia**

SARCLISA may cause neutropenia.

In patients treated with Isa-Pd, neutropenia occurred in 96% of patients and grade 3-4 neutropenia occurred in 85% of patients. Neutropenic complications occurred in 30% of patients, including febrile neutropenia (12%) and neutropenic infections (25%), defined as infection with concurrent grade ≥3 neutropenia. The most frequent neutropenic infections included infections of the upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%).

In patients treated with Isa-Kd, neutropenia occurred in 55% of patients, with grade 3-4 neutropenia in 19% of patients (grade 3 in 18% and grade 4 in 1.7%). Neutropenic complications occurred in 2.8% of patients, including febrile neutropenia (1.1%) and neutropenic infections (1.7%).

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

**Secondary Primary Malignancies**

The incidence of secondary primary malignancies is increased in patients treated with SARCLISA-containing regimens. The overall incidence of secondary primary malignancies in all SARCLISA-exposed patients was 3.6%.

In ICARIA-MM, secondary primary malignancies occurred in 3.9% of patients in the Isa-Pd arm and in 0.7% of patients in the Pd arm.

In IKEMA, secondary primary malignancies occurred in 7% of patients in the Isa-Kd arm and in 4.9% of patients in the Kd arm.

**NCCN Clinical Practice Guidelines in Oncology**

**for Multiple Myeloma**

(SARCLISA) as a Category 1 preferred option for early relapses (≥3 prior therapies)**

- In combination with pomalidomide and dexamethasone (after 2 prior therapies including lenalidomide and a PI)
- In combination with carfilzomib and dexamethasone

To see the data and for full Prescribing Information, visit sarclisahcp.com

The most common (≥1%) second primary malignancies in ICARIA-MM and IKEMA (N=329) included skin cancers (4% with SARCLISA-containing regimens and 1.5% with comparative regimens) and solid tumors other than skin cancer (1.8% with SARCLISA-containing regimens and 1.5% with comparative regimens). All patients with skin cancer continued treatment after resection of the skin cancer.

Monitor patients for the development of second primary malignancies.

**Laboratory Test Interference**

Interference with Serological Testing (Indirect Antiglobulin Test) SARCLISA binds to IgG on red blood cells (RBCs) and may result in a false-positive indirect antiglobulin test result. When SARCLISA is tested on RBCs that are antigen positive during Isad-Pd treatment in 68% of the tested patients, and during Isad-Kd treatment in 63% of patients. In patients with a positive indirect antiglobulin test, blood transfusions were administered without evidence of hemolysis. ABO/Rh typing was not affected by SARCLISA treatment.

Before the first SARCLISA infusion, conduct blood type and screen tests on SARCLISA-treated patients. Consider phenotyping prior to starting SARCLISA treatment. If treatment with SARCLISA has already started, inform the blood bank that the patient is receiving SARCLISA and that SARCLISA interference with blood compatibility testing can be resolved using dithiothreitol-treated RBCs. If an emergency transfusion is required, non–crossmatched ABO/Rh-compatible RBCs can be given as per local blood bank practices.

**Embryo-Fetal Toxicity**

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

**ADVERSE REACTIONS**

In combination with pomalidomide and dexamethasone: The most common adverse reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, pneumonia, and diarrhea. The most frequent hematologic laboratory abnormaliti es (≥5%) were decreased hemoglobin, decreased lymphocytes, and decreased platelets.

Serious adverse reactions occurred in ≥62% of patients receiving Isa-Pd. Serious adverse reactions in >5% of patients who received Isa-Pd included pneumonia (26%), upper respiratory tract infections (7%), and febrile neutropenia (7%). Fatel adverse reactions occurred in 11% of patients (those that occurred in more than 1% of patients were pneumonia and other infections (3%)).

Serious adverse reactions occurred in 59% of patients receiving Isa-Kd. The most frequent serious adverse reactions in >5% of patients who received Isa-Kd were pneumonia (25%) and upper respiratory tract infections (9%). Adverse reactions with a fatal outcome during treatment were reported in 3.4% of patients in the Isa-Kd group (those occurring in more than 1% of patients were pneumonia occurring in 1.7% and cardiac failure in 1.1% of patients).

**USE IN SPECIAL POPULATIONS**

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

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

Reference: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma v1.2022. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed August 24, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
4 CONTRAINDICATIONS

SARCLISA® is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients (see Warnings and Precautions [5.1]).

5.1 Infusion-Related Reactions

SARCLISA® is associated with a low incidence of infusion-related reactions.

6 WARNINGS AND PRECAUTIONS

5.1 Infusion-Related Reactions

SARCLISA® is associated with a low incidence of infusion-related reactions.

6.1 Relevant Interactions

SARCLISA® is metabolized by CYP3A4 and should be administered with caution in patients taking medications that are substrates or inhibitors of this enzyme.
**Table 4** summarizes the hematology laboratory abnormalities in ICARIA-MM.

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>SARCLISA® + Pomalidomide + Dexamethasone (Isa-Pd)</th>
<th>Pomalidomide + Dexamethasone (Pd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>(N=152)</td>
<td>(N=169)</td>
</tr>
<tr>
<td><strong>Laboratory Parameter</strong></td>
<td><strong>SARCLISA® + Pomalidomide + Dexamethasone (Isa-Pd)</strong></td>
<td><strong>Pomalidomide + Dexamethasone (Pd)</strong></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>99 32 0</td>
<td>97 28 0</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>96 24 61</td>
<td>92 38 31</td>
</tr>
<tr>
<td>Lympocytes decreased</td>
<td>92 42 13</td>
<td>92 35 8</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>64 14 16</td>
<td>79 9 19</td>
</tr>
</tbody>
</table>

The denominator used to calculate the percentage was based on the safety population.

Combination treatment with carfilzomib and dexamethasone (Isa-Kd)

The safety of SARCLISA was evaluated in IKEMA, a randomized, open-label clinical trial in patients with previously treated multiple myeloma. Patients received SARCLISA 10 mg/kg intravenously weekly for 3 weeks, followed by a 1-week break, for 6 cycles. The median age of the patients was 65 years old (range, 24–92). Of the 329 patients in the Isa-Kd subgroup (117 received isatuximab-irfc), 251 patients received >=1 SARCLISA infusion. In total, 99% of patients were exposed to SARCLISA for at least 6 months, and 96% were exposed to SARCLISA for 12 months or longer. The most common adverse reaction was infusion-related reactions (≥3% of patients who received Isa-Kd were affected). Most frequent serious adverse reactions in >5% of patients who received Isa-Kd were pneumonia (23%) and upper respiratory tract infections (9%). Adverse reactions with a total occurrence during treatment in ≥20% of patients in the Isa-Kd group (those occurring in more than 1% of patients were pneumonia occurring in 1.7% and cardiac failure in 1.1% of patients). Permanent discontinuation due to an adverse reaction (grade ≥4) occurred in 8% of patients who received Isa-Kd. The most frequent adverse reactions requiring permanent discontinuation in patients who received Isa-Kd were infections (2.8%). SARCLISA alone was discontinued in 0.6% of patients due to infusion-related reactions. Discharge intervals due to an adverse reaction occurred in 33% of patients who received SARCLISA. The most frequent adverse reaction requiring discharge interruption was infusion-related reaction (30%).

The most common adverse reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, fatigue, hypertension, diarrhea, pneumonia, dyspepsia, insomnia, bronchitis, cough, and back pain.

**Table 5** summarizes the adverse reactions in IKEMA.

**Table 5**: Adverse Reactions (≥10%) in Patients Receiving SARCLISA, Carfilzomib, and Dexamethasone with a Difference Between Arms of 2% or Greater Compared to Control Arm in IKEMA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SARCLISA® + Pomalidomide + Dexamethasone (Isa-Pd)</th>
<th>Pomalidomide + Dexamethasone (Pd)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Reactions</strong></td>
<td><strong>SARCLISA® + Pomalidomide + Dexamethasone (Isa-Pd)</strong></td>
<td><strong>Pomalidomide + Dexamethasone (Pd)</strong></td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td><strong>Infection-related</strong></td>
<td>46 0.6 0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>67 9 0</td>
<td>57 7</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>36 19 3.4</td>
<td>30 15 2.5</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>24 2 3</td>
<td>13 0.8</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>37 20 0.6</td>
<td>32 18 1.6</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysepsia</td>
<td>29 5 0</td>
<td>24 0.8</td>
</tr>
<tr>
<td>Cough</td>
<td>23 0 0</td>
<td>15 0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 2.8</td>
<td>0 29 2.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 1</td>
<td>1 9 0.8</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>35 10</td>
<td>32 3.3</td>
</tr>
</tbody>
</table>
| Infusion-related reaction includes infusion-related reaction, cytokine release syndrome, and hypersensitivity.
| Upper respiratory tract infection includes acute sinusitis, chronic sinusitis, HIV1 influenza, H1N1 influenza, influenza, lymphangitis, lymphangitis viral, nasopharyngeal, pharyngitis, pharyngolaryngitis, respiratory syncytial viral infection, rhinitis, sinusitis, sinusitis bacterial, tonsillitis. Meningitis, upper respiratory tract infection, viral meningitis, respiratory syncytial viral infection, influenza like illness, parainfluenza virus infection, respiratory tract infection bacterial, and viral upper respiratory tract infection.
| Pneumonia includes atypical pneumonia, lower respiratory tract infection, lower respiratory tract infection viral, pneumococcal pneumonia, pneumonia influenza, pneumococcal pneumonia leguminous, pneumococcal pneumonia respiratory syncytial viral, pneumococcal pneumonia viral, pulmonary edema, and pulmonary tuberculosis.
| Bronchitis includes bronchitis, bronchial viral, respiratory syncytial viral bronchitis, bronchitis chronic, and tracheobronchitis.
| Hypertension includes hypertension, blood pressure increased, and hypertensive crisis.
| Dysepsia includes dyspepsia and dyspepsia enterical.
| Cough includes cough, productive cough, and allergic cough.
| Fatigue includes fatigue and asthma.

**Table 6** summarizes the hematology laboratory abnormalities in IKEMA.

**Table 6**: Hematology Laboratory Abnormalities During the Period in Patients Receiving Isa-Pd versus Pd in IKEMA

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>SARCLISA® + Pomalidomide + Dexamethasone (Isa-Pd)</th>
<th>Pomalidomide + Dexamethasone (Pd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>(N=177)</td>
<td>(N=122)</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>99 22 0</td>
<td>99 20 0</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>94 52 17</td>
<td>95 43 14</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>94 19 11</td>
<td>88 16 8</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>55 18 1.7</td>
<td>43 7.8</td>
</tr>
</tbody>
</table>

The denominator used to calculate the percentage was based on the safety population.

**Description of Selected Adverse Reactions**

**Infusion-related reactions**

In ICARIA-MM, infusion-related reactions (defined as adverse reactions associated with the SARCLISA infusions, with an onset typically within 24 hours from the start of the infusion) were reported in 58% (382 treated with SARCLISA. All patients who experienced infusion-related reactions received aminophylline. The incidence of infusion-related reactions in patients treated with SARCLISA, with 3 patients (2%) also having infusion-related reactions at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 infusion-related reactions were reported in 3.9%, grade 2 in 36.7%, grade 3 in 13.7%, and grade 4 in 1.3% of the patients. Signs and symptoms of grade 3 or 4 infusion-related reactions included dyspnea, hypertension, and bronchospasm. The incidence of infusion interruptions because of infusion-related reactions was 30%. The median time to infusion interruption was 55 minutes. SARCLISA was discontinued in 2.6% of patients due to infusion-related reactions.
What’s Next for Real-World Evidence in Oncology?

MICHAEL VASCONCELLES, MD; AND BRAD JORDAN, PHD

CONTINUED FROM COVER

Why is it that the impact of RWD is growing and the convergence of clinical care and research is accelerating? Cancers are biologically complex and genetically heterogeneous. The ability to obtain optimal cancer care is impacted by social determinants within each patient’s environment, and today, access to care is uneven. Despite our recognition of these factors, the tools at our disposal to address each of them, be they diagnostic, therapeutic, or data and technologic, have been historically inadequate. These limitations have been compounded by well-intentioned social, health care, and regulatory policies that are incremental as measured against the scope of the challenge. For example, the bulk of what we’ve learned about how to treat cancer and the tremendous treatment advances over the last few decades are based on evidence generated from clinical trials centralized within academic medical centers and clinical research-focused practices and health systems. However, a minority of cancer care in the United States is actually delivered in these settings. We know that patients who receive care in these centers may not be fully representative of the broader population of patients with cancer, which may, in some cases, limit the generalizability of these data. The result may be barriers to enrollment in clinical trials of novel and potentially lifesaving cancer treatments and access to the resulting advanced diagnostics, therapies, or other interventions once they are approved.

In the United States, the digitalization of health care data accelerated in earnest more than 12 years ago with the passage of 2 critical pieces of federal legislation in short succession, the Health Information Technology for Economic and Clinical Health (HITECH) Act and the Affordable Care Act (ACA), both of which encouraged the meaningful use of electronic health records (EHRs). With the proliferation of EHRs designed to meet the requirements mandated within these statutes, the potential opportunities for broad uses of RWD were readily apparent. One example within oncology is Flatiron Health’s aggregation of deidentified real-world data sets derived from the medical records of more than 3 million US patients with cancer. Real-world use cases with these Flatiron Health data have included comparative effectiveness and outcomes research questions that contribute to improving our understanding of care delivery and its quality, the natural history of specific patient cohorts, use patterns, effectiveness, and adverse events of cancer medicines, among many others. The curation of both structured and unstructured data from EHRs involves a multifunctional team of clinical and technical experts, employing both human and machine-assisted components. These systems work together to create a deeply annotated research data set enhanced by the addition of composite or derived variables that can be linked to other data (eg, genomic and/or medical claims) to develop a highly comprehensive real-world data set.

A recent example of how RWD have contributed to improved care in the form of updated product labeling is the approval of a new dosing regimen for cetuximab, for use in certain patients with metastatic colorectal cancer (CRC) or squamous cell carcinoma of the head and neck.

A recent example of how real-world data have contributed to improved care in the form of updated product labeling is the approval of a new dosing regimen for cetuximab, for use in certain patients with metastatic colorectal cancer (CRC) or squamous cell carcinoma of the head and neck. In April 2021, the FDA approved a biweekly dosing regimen for cetuximab as an alternative to the previously approved weekly regimen. Real-world evidence (RWE) generated from RWD from patients receiving either the weekly or biweekly dosing regimen, including patient survival outcomes, supported the results of the population pharmacokinetic modeling analyses in the supplemental submission. The sponsor’s application was also supported by pooled analyses of overall response rates, progression-free survival, and overall survival from published literature focusing on patients with CRC and SCCCHN. An alternative, less-frequent cetuximab dosing regimen allows scheduling alongside other biweekly treatments, significantly reducing patient visit frequency to infusion centers. Time is a precious commodity for all of us, and even more so for patients with advanced cancer; every moment saved not traveling to and from the clinic, or being in the clinic, is a moment saved for living life.

This recent regulatory approval decision is one of several using RWD to provide evidence in the postapproval setting in support of regulatory decision-making, potentially obviating the need for expensive, difficult-to-acrue, and/or time-consuming clinical trials. This is only one recent example of how RWD and RWE can help drive progress in cancer treatments and have an impact on patient care. The effect that RWE can have in improving patients’ lives, such as the example with cetuximab above, is substantial, and in this fast-evolving field will be one of many in short order. However, innovations such as those that have facilitated the use of digital health care data to improve care require policies that
support and incentivize continued investment. The rapid pace of legislative initiatives with key digital health components, like the Prescription Drug User Fee Act VII reauthorization and the 21st Century Cures Acts (ie, Cures 1.0 and proposed 2.0), and the steady drumbeat of RWD/E-focused FDA Draft Guidance documents released since September 2021 are critical examples of how we’re meeting this need.

Flatiron Health, along with our colleagues in the RWE Alliance, commends the FDA for its efforts to advance the use of RWD/E for regulatory decision-making. For example, recent FDA Draft Guidance focusing on characterization of EHR data for use in developing RWE for regulatory decision-making is foundational to progressing toward more widespread generation and use of relevant, and reliable, RWE. We also welcome the provision in the proposed Cures 2.0 legislation for creation of an RWE Task Force to develop recommendations that encourage patients to participate in generating RWE, such as by joining postapproval clinical trials. These kinds of initiatives can help define ways that RWE can illuminate the effectiveness of drugs in the real world. This is important work, and it is critical that health technology and data companies, leaders in the RWE field for years, add their expertise to this evolution toward the wider use of RWD/E for regulatory decision-making.

Growing the footprint of clinical research beyond academic centers into the community oncology settings where most US patients with cancer are treated will help drive greater representativeness in the evidence used for important high-quality research, and for regulatory and treatment decisions. With this infrastructure and new tools that the field is working to put in place, it will be possible to use RWD to assess real-world effectiveness. Some of this proof-of-concept work is already being done with Health Technology Assessment bodies in Europe. RWD and RWE are here to stay and have enormous potential to accelerate the development of new drugs and improve cancer treatment and outcomes. We all need to work together to ensure that the infrastructure is in place to keep supporting and incentivizing continued innovation. Patients are counting on us.

**AUTHOR INFORMATION**

The authors are affiliated with Flatiron Health, a health care technology and services company focused on accelerating cancer research and improving care. Michael Vasconcellos, MD, is chief medical officer and head of the Medical and Scientific Organization at Flatiron Health. Brad Jordan, PhD, is senior director of Regulatory Affairs Policy at Flatiron Health and leads the company’s efforts to ensure an optimal regulatory environment in order to advance the use of real-world evidence. Flatiron Health is an independent affiliate of the Roche Group.

**REFERENCES**

Improving Diversity in Clinical Trials: How Early-Stage Investigators Are Reaching Underserved Populations

MATTHEW GAVIDIA

CONTINUED FROM COVER

Recently, the Bristol Myers Squibb Foundation (BMSF), in partnership with National Medical Fellowships and the American Association for Cancer Research, announced plans to address these issues by training early-stage investigators from the fields of oncology, hematology, cardiology, and immunology in essential community engagement research methods.

Five oncologists selected as part of the inaugural 52-physician cohort of BMSF’s Diversity in Clinical Trials Career Development Program spoke with Evidence-Based Oncology5 on what they seek to learn, on unmet needs that they see in patient populations of their respective studies, and how they would like to address the long-standing issue of diversity in clinical trials.

Being “Intentional” About Improving Patient Diversity in Clinical Trials
In caring for patients with breast cancer, which is the leading cause of cancer-associated mortality among Black females in the United States, Sonya Reid, MD, MPH, assistant professor, Division of Hematology/Oncology, Vanderbilt-Ingram Cancer Center, Nashville, Tennessee, seeks to address key disparities in outcomes among minority and underserved populations.

Currently, Black women with breast cancer have 5- and 10-year mortality rates that are double the rates of White women. Factors such as screening rates, stage at diagnosis, tumor biology, and social determinants of health have all been noted to influence patient outcomes.2

“We know social determinants of health are key factors that we need to address to get to the root of what is causing a lot of these disparities in breast cancer survival...less than 3% of patients who are accrued within breast cancer clinical trials are Black,” said Reid.

“Without improved racially diverse representation in these trials, oncology standards based primarily on non-Hispanic White patient data are at risk of not being generalizable. We see an underrepresentation of minority patients in prospective clinical trials as well as in genomic databases.”

In 2020, only 2% to 9% of participants included in clinical trials that led to FDA approval of 4 new breast cancer treatments were Black, with Hispanics accounting for 0% to 9% participation in those same trials.4 Moreover, significantly fewer studies of African, Latin American, and Asian ancestral populations have been identified within the genomic databases that are used for precision medicine research, in comparison with European populations.5

“This just speaks to the work that needs to be done,” said Reid. “We must be intentional about recruiting a diverse population in clinical trials to further understand the underpinnings of what’s causing these differences in cancer outcomes.”

Reid has been actively involved in breast cancer research in this country and, previously, in Jamaica, where she was raised and received her medical school training before moving to the United States. She expressed her enthusiasm about learning, through the BMSF program, how to not only execute, but also develop, clinical trials that are more community engaged, community focused, and patient focused. She is also excited about the opportunity to mentor and train medical students in community-based clinical research in the second year of the program.

Building trust within underserved communities to help ameliorate diversity issues in clinical trials will require careful attention, Reid said. “We know that 80% of cancer patients are treated not in academic centers, but in the community,” she explained. “I’m really looking forward to trying to understand the best practices as we develop clinical trials with that in mind from the beginning.”

Reid’s research primarily focuses on health disparities in breast cancer, with a particular interest in young-onset breast cancer and hereditary breast cancer. Specifically, she is investigating genomic differences that may be contributing to the racial survival disparity in breast cancer.

“We know social determinants of health are key factors that we need to address to get to the root of what is causing a lot of these disparities in breast cancer survival...less than 3% of patients who are accrued within breast cancer trials are Black.”

A Quest of Improve Outcomes Among Black Men With HIV and Cancer
In caring for patients with HIV and those at risk for HIV infection, Richard Silvera, MD, MPH, assistant professor, Infectious Disease, at Icahn School of Medicine at Mount Sinai, aims to improve medical outcomes for the Black community—particularly older Black men—by encouraging them to get tested for HIV as well as for anal cancer, a disease that is often overlooked in screening.

In the process of researching the connection between anal cancer and HIV, Silvera hopes to observe cells in an efficient, accessible way while educating and reaching out to the Black community.

Although Black individuals represent only 13% of the US population, they account for a significantly larger share of HIV diagnoses (43%), of people estimated to be living with HIV disease (42%), and deaths among people with HIV (44%) than any other racial group in the nation.8

For populations with HIV, particularly men of color who have sex with men (MSM), Silvera noted the substantial risk posed by human papillomavirus (HPV), the most common sexually transmitted disease worldwide, in leading to the development of anal cancer.

Research has shown that HIV increases the risk of HPV infection and the development of abnormal cells that cause anal cancer, namely high-grade anal intraepithelial neoplasia or high-grade squamous intraepithelial lesions. These lesions are much more likely to occur in MSM populations, older individuals, and those with compromised immune systems.7

“All those problems kind of interact with each other in a somewhat complicated way. We know that people of color are overrepresented among people with HIV. We know that HIV...
is a medical problem that people of color have to face, and that's due to structural inequities, history, and all sorts of other things,” said Silvera.

While studying English in college, Silvera's interest in HIV was piqued during a course that covered literature on HIV and AIDS. He learned that HIV's impact was not only biological, but had political, economic, and social implications as well.

“I wanted to have research be a big component of what I did going forward, because research is kind of a way of taking individual people's stories and putting them together to affect whole groups of people,” Silvera recalled.

Because anal cancer incidence is markedly higher among people with HIV than in the general population, and even more so among MSM populations and older people, Silvera seeks to prioritize the representation of these at-risk groups in clinical trials.

Moreover, Silvera said, he is looking forward to learning more about the structure of clinical trials and how to be a successful researcher through the BMSF program—skills that may not be easily honed by those without access to social or mentoring networks, he noted.

“As a gay Black man myself, I want to try to bring that perspective and that experience into this research, because there will be insights that you just cannot learn in a book,” Silvera said. “I think you need this diverse perspective to have it all—aspects of both those who are experiencing this disease, as well as those who are trying to cure it or treat it.”

Taking on Health Care Disparities in the Rural South
An Afro-Latina and the first physician in her family, Analiz Rodriguez, MD, PhD, director, Neurosurgical Oncology, University of Arkansas for Medical Services in Little Rock, has known since the third grade that she wanted to be a neurosurgeon and help minority and marginalized communities.

These pursuits led her to the state of Arkansas, which ranks sixth-worst in the nation for cancer mortality rate. As a neurosurgeon-scientist specializing in brain tumors, Rodriguez strives to bring novel therapies and clinical trials to the rural South.

“I think that I chose to practice in the rural South for many reasons—one key reason is that I feel the health care disparities are just more apparent. I also very much enjoy working with rural patients,” said Rodriguez.

“My goal in coming to Arkansas was to provide cutting-edge research and treatments for patients through clinical trials,” she explained. “I fundamentally do not believe that it’s fair that you should die from cancer earlier than other people based on your zip code, the color of your skin, or what language you speak.”

Her academic center is the only one of its kind in Arkansas, so access to higher-level cancer care—such as immunotherapy—remains unavailable to many of the state's residents. In particular, high rates of poverty and lack of access to health care have been reported in the mostly rural Eastern part of the state, known as the Arkansas Delta, which includes 4 of the 5 Arkansas counties with the highest rate of cancer. One of these, Monroe County, has the highest rate of cancer deaths in the state, at 249.5 deaths per 100,000.

Rodriguez said she plans to leverage the lessons gained from the BMSF program in building clinical trials to improve access for certain communities that have been underserved historically, particularly Black Americans; they make up a higher share of the population in Southern states than in many other locations in the country.

She's also interested in investigating how lifestyle may impact the immune microenvironment and patient response to certain therapies.

“Our country is very much segregated. We have a lot of places where there are food deserts. And if you live in a certain area, and you don’t have access to certain types of food, because of your environment, you may have a different outcome in regard to your cancer.

Rodriguez said studying the same types of people—those who are more affluent, while leaving out minorities and those from rural areas—will mean that some questions will go unstudied and unanswered.

“We have a lot of technology, a lot of resources. It just doesn’t make sense that we’re still having this conversation in 2022, but let’s get rid of this problem and move forward.”

In her clinical research, Rodriguez hopes to observe cancer models and learn how the disease affects a wide range of populations by both race and location.

A Pediatric Hematologist/Oncologist Hopes to Build Trust in Her Community
Raised by Mexican immigrant parents in East Los Angeles, Sonia Morales, MD, pediatric hematologist-oncologist, Children’s Hospital of Orange County, California, learned early, from her own health experiences, about the physical and mental challenges pediatric patients face in managing lifelong diseases.

Diagnosed with optic glioma as a child, the trajectory of her patient journey fueled Morales' interest in medicine and led to a career in pediatrics specializing in hematology-oncology.

For the more than 500,000 pediatric cancer survivors in the United States today, Morales noted that the transition from a child’s hospital to adult care can complicate adherence to many long-term follow-up needs. These include, to start, screening for secondary malignancies or osteopenia, mental health counseling for developmental concerns, and addressing posttraumatic stress disorder—and this is all especially true for underserved groups like Hispanic and other minority survivors.

“Minority populations are already at risk for poor health outcomes due to socioeconomic inequities and health disparities. A lot of our patients are not in affluent areas or areas where there are academic centers, so there’s decreased availability of clinical trials,” said Morales.

“The overall survival in Hispanic children for some reason—potentially due to genetics, and we’ve heard about zip codes affecting your health as well—is not as good as in their White counterparts.”

Research results have indicated that, compared with White children, Black children are between 38% and 95% more likely to die of several types of cancer, and Hispanic children were between 31% and 65% more likely to die.12 Socioeconomic status was shown to significantly mediate the racial/ethnic disparities in surviving childhood cancers, including acute lymphoblastic leukemia, acute myeloid leukemia, neuroblastoma, and non-Hodgkin lymphoma.

“In order to work toward equity, we need to start drawing more information from our disadvantaged communities, those that we're not normally representing in our research samples,” emphasized Morales. She is excited that her penchant for career growth and development dovetail with the opportunity presented by the BMSF program to be paired with like-minded individuals of similar backgrounds who all share the same goals: improving health equity and eliminating existing disparities.

Ensuring representation of underserved Hispanic and minority populations in future clinical trials is key to reducing sample bias and providing data that better reflect the whole US population, said Morales. Adolescents and young adult populations in general are already understudied in research, making efforts to include younger members of minority communities even more crucial.13

“We need trust in the community. We also need our communities to feel like they’re helping us with research and also that they’re guiding the research… I think gone are the days where we go and tell the community what they need,” Morales pointed out. “I think we should start striving to learn from our patients.”

Sonia Morales, MD, pediatric hematologist-oncologist, Children’s Hospital of Orange County, California.

Beatris Wille-Sanin, MD, clinical fellow, Hematology and Oncology, Memorial Sloan-Kettering Cancer Center
learn from the families, and try to gauge more of what their needs are, and then work together to develop interventions.”

Morales’ research seeks to help families fully understand their cancer diagnoses, treatment plans, and survivorship roadmaps.

**Improving Clinical Trial Diversity Means Building a Willingness to Participate**

Born in Bogota, Colombia, Beatriz Wills-Sanin, MD, clinical fellow, Hematology and Oncology, Memorial Sloan Kettering Cancer Center, New York, New York, first became passionate about increasing diversity in clinical trial research while working in underserved Colombian communities during medical school.

As she became exposed to different pathologies and patients of diverse race/ethnicity and background, Wills-Sanin found that the lack of access to centralized care in these communities, particularly in regard to cervical cancer screening and HPV vaccination, influenced her decision to pursue a career in medical oncology.

Then, through her subsequent residency at the Johns Hopkins School of Public Health, she learned that improving diversity in clinical trials concerns not only access, but the willingness among minority patients to participate. “I learned about how many patients visualize health care and clinical trials in the community. For instance, even speaking about lung cancer screening was kind of a taboo for these patients, because many viewed clinical trials or participation in any screening or routine clinical practice as an experiment rather than standard of care,” said Wills-Sanin.

Prior events such as the Tuskegee syphilis study continue to arouse suspicion of clinical trials for Black Americans, and discrimination and language barriers can also exacerbate mistrust in the medical system for minorities.14

“Building community outreach to ‘people in underserved’ areas who would not otherwise have access is very important. One of the things that we did in medical school other than screening is education—doing focus groups about lung cancer screening and Pap smears, as well as the importance of just taking care of yourself and having a primary care physician.”

In learning about clinical trial design through the BMSF program, Wills-Sanin noted that one of the biggest factors addressed so far is eligibility. Prior events such as the Tuskegee syphilis study continue to arouse suspicion of clinical trials for Black Americans, and discrimination and language barriers can also exacerbate mistrust in the medical system for minorities.14

“How Each Investigator Would Address Diversity in Clinical Trials

“‘We have to be intentional in our clinical trial design, as well as give support—whether that be academic community partnerships or supporting those smaller centers that may not be as research heavy—to build up their clinical research infrastructure,’” said SONYA REID, MD, MPH.

“I think an important thing for bringing diversity into the workforce is having clinical research be a concept introduced earlier in education. I think it will lead to more diverse groups of people coming into research, and I also think it will let people know that they can be a researcher,” said RICHARD SILVERA, MD, MPH.

“I feel that the workforce diversity among physicians needs to be increased in order to help address some common challenges that limit accrual of people who have been historically excluded in clinical trials. This includes language barriers, not having medical trial consent forms in other languages, and not understanding how to revamp certain processes with the appropriate cultural context,” said ANALIZ RODRIGUEZ, MD, PHD.

“‘Increasing diversity in your workforce and getting community engagement, community participation, at the initiation of your trial—even when you’re designing trials. That will help in building trust within our communities that are not always so trusting of the health care system. The more they see individuals like yourself that are of similar backgrounds, the more willing they will be to participate in research and clinical trials,’” said SONIA MORALES, MD.

“I think that opening sites in different hospitals and building up multi-institutional collaborations is essential to be able to improve diversity in clinical trial accrual. Primary care physicians should be available to all of the community, not only those patients who are near big cities and huge academic hospitals, but [those throughout] the whole country,” said BEATRIZ WILLS-SANIN, MD.

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**REFERENCES**


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**HEALTH EQUITY**

Now in advanced clinical training for hematologic malignancies, with a special interest in lymphoma, Wills-Sanin seeks to investigate new opportunities for immunotherapy in cutaneous T-cell lymphoma and improve understanding of racial disparity in lymphoma.
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