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THERAPEUTIC ADVANCES

Data Sharing From Cancer Drug Trials Falls Short of Promises, Study Authors Say
Mary Caffrey

THE PRECISION MEDICINE ERA promises treatments for cancer and other diseases will be increasingly tailored to a patient’s individual traits. That may mean finding therapies that target certain genes or proteins or using data to learn which regimens work best given a patient’s sex, ethnicity, age, or other factors.

As study results are reported, some answers seem clear; others, less so. Results of a study published in May found that women in cancer clinical trials are far more likely than men to experience adverse events (AEs) from drug toxicity. Meanwhile, investigators of a study published in 2021 asked whether different pharmacokinetic responses were due to ethnic differences or to factors such as age, diet, and other medicines patients were taking.

One thing is certain: answering these questions requires more data, not less. And that’s why investigators from Australia sounded the alarm with results from an audit published in the September issue of JAMA Oncology. They found that individual participant data (IPD) from 55% of the cancer clinical trials that led to FDA approvals over a 10-year period are not available to independent investigators, despite a 2014 pledge from the pharmaceutical industry to improve data transparency.

Lead author and PhD candidate Natansh D. Modi, BPharm; and senior author Ashley M. Hopkins, PhD, both of the College of Medicine and Public Health at Flinders University in Adelaide, Australia, told Evidence-Based Oncology (EBO) in an interview how the audit was triggered by their individual frustrations in seeking trial data for other projects.

INTERVIEW

COA’s Bo Gamble: Slowing Down, but Not Stepping Away From Bringing Quality to Cancer Care
Interview by Mary Caffrey

BO GAMBLE, THE LONGTIME DIRECTOR of strategic practice initiatives at the Community Oncology Alliance (COA) and a go-to person for all things value-based care, will soon step down from his full-time role. Gamble was honored on October 24, 2022, at the COA Payer Exchange Summit in Tysons Corner, Virginia, for his service to the organization and his work to bring transformation to cancer care.

Gamble, who joined COA full-time in May 2011, will be transitioning to part-time status on January 1, 2023, when he will begin mentoring 2 new staff members taking on COA initiatives. Gamble will also work with the American Society of Clinical Oncology (ASCO) to implement the Oncology Medical Home (OMH) ASCO Patient-Centered Cancer Care Certification (APC4) program, a joint project of ASCO and COA. Gamble helped develop the program using OMH standards and a systemic evidence review; the review panel toured cancer centers to evaluate how well they met the standards.

COMMENTARY

PBM Fees Put the “GER” in Danger for Specialty Pharmacies
Darrell L. Willyard, PharmD; and Alexis V. Fanshier, BA

SHOULD MEDICALLY INTEGRATED specialty pharmacies (MIPs) be forced to lose money in order to serve their patients? What if a pharmacy would lose more than $10,000 by filling a single prescription?

Many MIPs face this situation because of a direct and indirect remuneration (DIR) fee known as a generic fee (GER).

Interview by Mary Caffrey

Continued on SP591 »

Continued on SP592 »

Continued on SP594 »
INDICATIONS
IMBRUVICA® (ibrutinib) is a kinase inhibitor indicated for the treatment of adult patients with:
• Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL).
• CLL/SLL with 17p deletion.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
Hemorrhage: Fatal bleeding events have occurred in patients who received IMBRUVICA®. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuitis, and post procedural hemorrhage) occurred in 4.2% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA® in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA®, respectively. The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA® without anticoagulant or antiplatelet therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding.

Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients who received IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jiroveci pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

Cardiac Arrhythmias, Cardiac Failure, and Sudden Death: Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA®. Deaths due to cardiac causes or sudden deaths occurred in 1% of 4,896 patients who received IMBRUVICA® in clinical trials, including in patients who received IMBRUVICA® in unapproved monotherapy or combination regimens. These adverse reactions occurred in patients with and without preexisting hypertension or cardiac comorbidities. Patients with cardiac comorbidities may be at greater risk of these events.

Grade 3 or greater ventricular tachyarythmias were reported in 0.2%, Grade 3 or greater atrial fibrillation and atrial flutter were reported in 3.7%, and Grade 3 or greater cardiac failure was reported in 1.3% of 4,896 patients who received IMBRUVICA® in clinical trials, including in patients who received IMBRUVICA® in unapproved monotherapy or combination regimens. These events have occurred particularly in patients with cardiac risk factors including hypertension and diabetes mellitus, a previous history of cardiac arrhythmias, and in patients with acute infections.

Evaluate cardiac history and function at baseline, and monitor patients for cardiac arrhythmias and cardiac function. Obtain further evaluation (e.g., ECG, echocardiogram) as indicated for patients who develop symptoms of arrhythmia (e.g., palpitations, lightheadedness, syncope, chest pain), new onset dyspnea, or other cardiovascular concerns. Manage cardiac arrhythmias and cardiac failure appropriately, follow dose modification guidelines, and consider the risks and benefits of continued IMBRUVICA® treatment.

Hypertension: Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 6% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.63 to 24 months). Monitor blood pressure in patients treated with IMBRUVICA®, initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate, and follow dosage modification guidelines for Grade 3 or higher hypertension.
LIVING LONGER IN 1L CLL

OUTCOMES FROM THE RESONATE™-2 TRIAL
EVALUATING IMBRUVICA® VS CHLORAMBUCIL

PROGRESSION-FREE SURVIVAL WAS THE PRIMARY ENDPOINT, OVERALL SURVIVAL WAS A SECONDARY ENDPOINT

RESONATE™-2 study design
Phase 3, multicenter, open-label trial of 1L CLL/SLL patients (N=269) ≥65 years of age who were randomized 1:1 to IMBRUVICA® 420 mg once daily until disease progression or unacceptable toxicity (n=136) or CIB (n=133) for up to 12 cycles. Patients with del17p were excluded. The primary endpoint was PFS as assessed by an IRC per iwCLL criteria (primary analysis). OS was a secondary endpoint. Patients with IR-confirmed disease progression were enrolled in an extension study (long-term follow-up) and second-line treatment per investigator’s choice (including IMBRUVICA® for patients progressing on chlorambucil).

Most common ARs (median duration of exposure for IMBRUVICA®: 17.4 months, n=135)
- The most common ARs (all grades) occurring in ≥15% of patients receiving IMBRUVICA® were neutrophils decreased (55%), platelets decreased (47%), diabetes (42%), hemorrhage (39%), musculoskeletal pain (38%), fatigue (30%), cough (22%), nausea (22%), rash (21%), bruising (19%), peripheral edema (19%), dry eye (17%), pyrexia (17%), upper respiratory tract infection (17%), arthralgia (16%), constipation (16%), and skin infection (15%)
- The most common grade ≥3 ARs (grades ≥3) occurring in patients receiving IMBRUVICA® were neutrophils decreased (28%), pneumonia (18%), platelets decreased (17%) and bruising (17%)

Please see Brief Summary of full Prescribing Information on the following pages.
IMBRUVICA® (ibrutinib)

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect patients, 87% were exposed for 6 months or longer and 68% were exposed for greater than one year; once daily (174 patients), and in 4 trials administered in combination with other drugs at 420 mg orally clinical trials of another drug and may not reflect the rates observed in practice. The pooled safety Because clinical trials are conducted under widely variable conditions, [see Warnings and Precautions]

Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 23% of 1,476 patients who received IMBRUVICA in clinical trials (see Adverse Reactions). Infections were reported in patients with cardiovascular risk factors including hypertension and diabetes mellitus, a previous history of cardiac arrhythmias, and in patients with acute infections (see Adverse Reactions).

Evaluate cardiac history and function at baseline, and monitor patients for cardiac arrhythmias and cardiac function. Obtain further evaluation (e.g., ECG, echocardiogram) as indicated for patients with cardiac risk factors (see Warnings and Precautions). Monitor complete blood counts monthly.

When grade 3 or higher, repeat dosing should not resume until all adverse reactions have resolved to baseline with at least 2-weeks of time since the reaction was reported. The most frequent secondary malignancy was non-melanoma skin cancer (6%).

Tumor Regrowth: Tumor lysis syndrome has been infrequently reported with IMBRUVICA (see Adverse Reactions). Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions (e.g., hydration and treatment close to as a prophylaxis).

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibritinib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2-20 times higher than those reported in pregnant women with hematologic malignancies. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose. (see Use in Specific Populations).

ADVERSE REACTIONS

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

• Hemorrhage [see Warnings and Precautions]

• Infections [see Warnings and Precautions]

• Cardiac Arrhythmias, Cardiac Failure, and Sudden Death [see Warnings and Precautions]

• Hypersensitivity [see Warnings and Precautions]

• Cytophenias [see Warnings and Precautions]

• Second Primary Malignancies [see Warnings and Precautions]

• Tumor Regrowth [see Warnings and Precautions]

Clinical Trials Experience: Because clinical trials are conducted under widely variable conditions, adverse reactions observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice. The pooled safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to IMBRUVICA in 6 trials in 1,476 patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The most frequent adverse reactions of at least 2% in patients with CLL/SLL treated with IMBRUVICA are listed in Table 5.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm

<table>
<thead>
<tr>
<th>Body System</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruising</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Rashes</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>11</td>
<td>0</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
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<td></td>
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<tr>
<td>Musculoskeletal pain</td>
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<td>0</td>
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<tr>
<td>Muscle spasms</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dorsal pain</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neoplasms benign, malignant, unspecified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second malignancies</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

<table>
<thead>
<tr>
<th>Body System</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>20</td>
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</tr>
<tr>
<td>Stomatitis</td>
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<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruising</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Rashes</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dorsal pain</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neoplasms benign, malignant, unspecified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second malignancies</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect the most common adverse reactions (≥30%) were thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, and respiratory infections. In patients who received IMBRUVICA, 87% were exposed for 6 months or longer and 68% were exposed for greater than one year; subjects with multiple events for a given ADR term are counted once only for each ADR term. The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm. * Includes multiple ADR terms.

Treatment-emergent Grade 4 thrombocytopenia (1% in the IMBRUVICA arm vs 3% in the chlorambucil arm) and neutropenia (11% in the IMBRUVICA arm vs 12% in the chlorambucil arm) occurred in patients. HELIOS: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in HELIOS in patients with previously treated CLL/SLL.

<table>
<thead>
<tr>
<th>Table 5: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2 (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body System Adverse Reaction</td>
</tr>
<tr>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body System Adverse Reaction</td>
</tr>
<tr>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
</tr>
<tr>
<td>Platelets decreased</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms.

** Includes 3 events of pneumonia with fatal outcome in each arm, and 1 event of pyrexia and upper respiratory tract infection with a fatal outcome in the ofatumumab arm.

** Includes multiple ADR terms.

** Includes 2 events of hemorrhage with fatal outcome in the IMBRUVICA arm and 1 event of neutropenia with a fatal outcome in the placebo + BR arm.

** Includes multiple ADR terms.

<table>
<thead>
<tr>
<th>Table 7: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2</th>
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<tbody>
<tr>
<td>Body System Adverse Reaction</td>
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<tr>
<td>All Grades (%)</td>
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<tr>
<td>Nervous system disorders</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 8: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in ILLUMINATE</th>
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</thead>
<tbody>
<tr>
<td>Body System Adverse Reaction</td>
</tr>
<tr>
<td>All Grades (%)</td>
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<td>Blood and lymphatic system disorders</td>
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<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
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</tbody>
</table>
Table 8: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE (continued)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>IMBRUVICA + Ominostomab (N=113)</th>
<th>Chlorambucil + Ominostomab (N=115)</th>
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</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td></td>
<td>Groin pain*</td>
<td>33 1 23 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arthropalgia</td>
<td>22 1 10 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>13 0 8 0</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>27 1 12 0</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>Hemorrhage*</td>
<td>25 1 9 0</td>
<td></td>
</tr>
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<td></td>
<td>Hypertension*</td>
<td>17 4 4 3</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
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<tr>
<td></td>
<td>Hyperuricemia</td>
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<td></td>
<td>Atrial fibrillation</td>
<td>12 5 0 0</td>
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<tr>
<td>Psychiatric disorders</td>
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<tr>
<td></td>
<td>Somnolence</td>
<td>12 0 4 0</td>
<td></td>
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</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms.

† Includes one event with a fatal outcome.

E1912: Adverse reactions described below in Table 9 reflect exposure to IMBRUVICA + rituximab with a median duration of 34.3 months and exposure to FCR with a median of 4.7 months in E1912 in patients with previously untreated CLL/SLL who were 70 years or younger.

Table 9: Adverse Reactions Reported in ≥ 15% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in E1912

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>IMBRUVICA + Rixutimab (N=202)</th>
<th>Fludarabine + Cyclophosphamide + Rixutimab (N=150)</th>
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<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>80 2 78 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>28 1 17 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>27 1 27 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>23 2 8 0</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Muscle pain*</td>
<td>61 5 35 2</td>
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<td></td>
<td>Arthropalgia</td>
<td>41 5 10 1</td>
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<td>Gastrointestinal disorders</td>
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<td></td>
<td>Diarrhea</td>
<td>53 4 27 1</td>
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<tr>
<td></td>
<td>Nausea</td>
<td>40 1 64 1</td>
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<tr>
<td></td>
<td>Stomatitis*</td>
<td>22 1 9 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal pain*</td>
<td>19 2 10 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>18 2 28 0</td>
<td></td>
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<tr>
<td></td>
<td>Constipation</td>
<td>17 0 32 0</td>
<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
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<td>Hypertension*</td>
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<td>Hemorrhage*</td>
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<td>Nervous system disorders</td>
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<td>Seizure</td>
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<td>Dizziness</td>
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<td>Peripheral neuropathy*</td>
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Based on laboratory measurements per IWGCLL criteria.

Additional Important Adverse Reactions: Cardiovascular Events: Data on cardiovascular events are based on randomized controlled trials with IMBRUVICA (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm). The incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.8% versus 3.8% and of Grade 3 or greater was 0.3% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. The incidence of atrial fibrillation and atrial flutter of any grade was 8.4% versus 16% and for Grade 3 or greater was 4.9% versus 0.5% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of cardiac failure of any grade was 1.7% versus 0.0% and for Grade 3 or greater was 1.2% versus 0.3% in patients treated with IMBRUVICA compared to patients in the control arm.

The incidence of ischemic cerebrovascular events (cerebrovascular accidents, ischemic stroke, cerebral ischemia, and transient ischemic attack) of any grade was 1.5% versus 0.4% and of Grade 3 or greater was 0.5% versus 0.2% in patients treated with IMBRUVICA compared to patients in the control arm, respectively.

Diarrhea: In randomized controlled trials (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm), diarrhea of any grade occurred at a rate of 43% of patients treated with IMBRUVICA compared to 19% of patients in the control arm. Grade 3 diarrhea occurred in 2% versus 0% in IMBRUVICA-treated patients compared to the control arm, respectively. Less than 1% (0.3%) of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

Based on data from 1,665 of these patients, the median time to first onset was 21 days (range, 0 to 704) versus 46 days (range, 0 to 492) for any grade diarrhea and 117 days (range, 3 to 414) versus 194 days (range, 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 85% versus 89% had complete resolution, and 15% versus 11% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated patients was 7 days (range, 1 to 815) versus 4 days (range, 1 to 367) for any grade diarrhea and 7 days (range, 1 to 78) versus 19 days (range, 1 to 56) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively.

Visual Disturbances: In randomized controlled trials (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm), blurred vision and decreased visual acuity of any grade occurred in 11% of patients treated with IMBRUVICA (9.5% in Grade 2 and 2% in Grade 3) versus 7% in the control arm (5.2% in Grade 1, 2% in Grade 2, and 3% in Grade 3).

Based on data from 1,605 of these patients, the median time to first onset was 91 days (range, 0 to 671) versus 100 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution was 37 days (range, 1 to 457) versus 26 days (range, 1 to 721) in IMBRUVICA-treated subjects compared to the control arm, respectively.

Long-Term Safety: The safety data from long-term treatment with IMBRUVICA over 5 years of 1,284 patients (treatment naive CLL/SLL n=192) were reevaluated (refractory CLL/SLL n=466, relapsed/refractory MCL n=370, and WM n=108) were analyzed. The median treatment duration was 51 months (range, 0.2 to 96 months) for CLL/SLL, 11 months (range, 0 to 87 months) for MCL, and 43 months (range, 0.3 to 61 months) for WM. The cumulative rate of hypertension increased over time. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 7% (year 1-2), 9% (year 2-3), 9% (year 3-4), and 9% (year 4-5); the overall incidence for the 5-year period was 11%.

IMBRUVICA® (ibrutinib)
Postmarketing Experience: The following adverse reactions have been identified during postapproval use of IMBRUVICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hepatobiliary disorders: hepatic failure including acute and/or fatal events, hepatic cirrhosis
- Respiratory disorders: interstitial lung disease
- Cardiac disorders: pericarditis and pericardial effusion

immune system disorders: tumor lysis syndrome
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), oxynochloïdes, panniculitis, neurophilic dermatoses
- Infections: hepatitis B reactivation
- Nervous system disorders: peripheral neuropathy

DRUG INTERACTIONS

Effect of CYPREA Inhibitors on Ibrutinib: The coadministration of IMBRUVICA with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

Dose modifications of IMBRUVICA are recommended when used concomitantly with pasacnazoline, voriconazole and moderate CYP3A inhibitors [see Dosage and Administration (2.3) in Full Prescribing Information]. Avoid concomitant use of other strong CYPREA inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) [see Dosage and Administration (2.3) in Full Prescribing Information].

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYPREA.

Effect of CYPREA Inducers on Ibrutinib: The coadministration of IMBRUVICA with strong CYPREA inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYPREA inducers [see Clinical Pharmacology (12.3) in Full Prescribing Information].

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary: IMBRUVICA can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused a decrease in fetal weight and increased resorptions and post-implantation loss. The dose of 8 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or marginal zone lymphoma (MCL) and 20 times the exposure in patients with CLL/SLL. At 25 mg/kg/day in rabbits, ibrutinib administered the dose of 570 mg daily and 430 mg daily, respectively. ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL and the administered dose of 560 mg daily and 430 mg daily, respectively. ibrutinib was administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. ibrutinib at a dose of 15 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 20 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 mg daily and 430 mg daily, respectively.

Lactation: Risk Summary: There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with IMBRUVICA and for 1 week after the last dose.

Females and Males of Reproductive Potential: IMBRUVICA can cause fetal harm when administered to pregnant women [see Use in Specific Populations].

Contraceptive: Verify pregnancy status in females of reproductive potential prior to initiating IMBRUVICA.

Contraception: Females: Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose.

Males: Advise males with female partners of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month following the last dose.

Pediatric Use: Mature B-cell Non-Hodgkin Lymphoma: The safety and effectiveness of IMBRUVICA in combination with chemotherapy were assessed but have not been established based on an open-label, randomized study (NCT02023725) in 35 patients, which included 26 pediatric patients age 5 to 17 years, with previously treated mature B-cell non-Hodgkin lymphoma. The study was stopped for futility. In the randomized population, major hemorrhage and discontinuation of chemotherapy due to adverse reactions occurred more frequently in the ibrutinib plus chemotherapy arm compared to the chemotherapy alone arm.

CLL/SLL/WM: CLL/SLL/WM with 17p deletion. WM: MCL: The safety and effectiveness of IMBRUVICA in pediatric patients have not been established in MCL, CLL/SLL, CLL/SLL with 17p deletion, WM, MCL, and and/or MZL. Geriatric Use: Of the 1,124 patients in clinical studies of IMBRUVICA for MCL, CLL/SLL, CLL/SLL with 17p deletion, WM, MCL, and and/or MZL, 64% were ≥ 65 years of age, while 23% were >75 years of age (see Clinical Studies (14)). No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades), granulocytopenia (grade 3 or higher), thrombocytopenia, hypertension, and atrial fibrillation occurred more frequently among older patients treated with IMBRUVICA (see Adverse Reactions).

Hepatic Impairment: Adult Patients with B-cell Malignancies; Avoid use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment (Child-Pugh class A). Reduce the recommended dose when administering IMBRUVICA to patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients more frequently for adverse reactions of IMBRUVICA [see Dosage and Administration (2.4), Clinical Pharmacology (12.3) in Full Prescribing Information].

Plasmapheresis: Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

IMBRUVICA® (ibrutinib)

PATIENT COUNSELING INFORMATION

Advises the patients and caregivers to read the FDA-approved patient labeling (Patient Information).

Hemorrhage: Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures [see Warnings and Precautions].

Infections: Inform patients of the possibility of serious infection, and to report any signs or symptoms suggestive of infection (see Warnings and Precautions).

Cardiac arrhythmias: cardiac failure, and sudden death: Inform patients of the possibility of irregular heart rhythm, heart failure and sudden death. Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, chest discomfort, or edema [see Warnings and Precautions].

Hypertension: Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy (see Warnings and Precautions).

Second primary malignancies: Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas (see Warnings and Precautions).

Tumor lysis syndrome: Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation (see Warnings and Precautions).

Embro-fetal toxicity: Advise women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy for evaluation (see Warnings and Precautions).

Second primary malignancies: Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas (see Warnings and Precautions).

Tumor lysis syndrome: Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation (see Warnings and Precautions).

Other Important Information: Inform patients to take IMBRUVICA orally once daily according to their prescribing information and that the oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or tablets, crushing or chewing the tablets approximately the same time each day (see Dosage and Administration (2.1) in Full Prescribing Information).

Advises patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose (see Dosage and Administration (2.1) in Full Prescribing Information).

Advises patients of the common side effects associated with IMBRUVICA (see Adverse Reactions). Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.

Advises patients to inform their healthcare provider of all prescription medicines, over-the-counter drugs, vitamins, and herbal products (see Drug Interactions).

Advises patients that they may experience loose stools or diarrhea and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration (see Adverse Reactions).

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Turning Points in Community Oncology

This issue of Evidence-Based Oncology™ (EBO) is filled with examples of innovation at every level of community oncology, from award-winning ideas presented at the National Oncology Conference of the Association of Community Cancer Centers to the concepts shared during the fall meetings of our Institute for Value-Based Medicine® (IVBM).

What excites us? Our meeting with Rocky Mountain Cancer Centers explored their use of an evaluation tool to weigh the risks of chemotherapy in certain high-risk patients. At our meeting with Astera Cancer Care, CEO Edward J. Licitra, MD, PhD, described his work on a first-of-its-kind episode-of-care model that could significantly reduce the cost chimeric antigen receptor T-cell therapy when delivered in community clinics, making this lifesaving treatment accessible to more patients.

But these success stories are balanced by headwinds from Medicare, which has slashed payments to physician-owned practices by 4.5% for 2023 while increasing payments to hospital-owned entities. This continued pummeling of community oncology threatens its future. It comes despite a recent investigation by The New York Times of how a Virginia health system abused the 340B program when it hollowed out an urban hospital until it was essentially an emergency room, leaving the hospital without necessary services to care for patients with COVID-19.

OneOncology CEO Jeff Patton, MD, cited the Times investigation at the network’s first physician leadership conference in Nashville, Tennessee, which is covered in this issue. Patton said that for the first time in a while, he had hope that 340B reform is possible. But there’s much work to be done, as former Obama administration official Kavita Patel, MD, told the group. A major challenge, she said, is that the people writing the payment rules at Medicare lack a basic understanding of the realities of finances at a community oncology practice. It’s essential for community oncology providers to demand a seat at the table as the fine points of the Inflation Reduction Act of 2022 are implemented so that well-intentioned pieces such as negotiated drug prices or a cap on seniors’ out-of-pocket costs don’t come out of the bottom line of physician-owned practices.

All these topics will be on the agenda going into 2023 as we plan a full schedule of IVBM sessions across the country starting in January. IVBM has 2023 as we plan a full schedule of IVBM sessions across the country starting in January. IVBM has

Sincerely,
Mike Hennessy Sr
President & CEO
**EVIDENCE-BASED ONCOLOGY™**

**DECEMBER 2022**

**Volume 28, Issue 8**

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Cancer Payment Models Improve Care, but Making Them Work Takes Effort
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Innovation in a Time of Scarcity

WE LIVE IN A TIME of life-changing innovation in cancer care that almost defies the imagination. Over the last 16 years, The Cancer Genome Atlas Program has added “2.5 petabytes of genomic, epigenetic, transcriptomic, and proteomic data” to our oncology knowledge database.1 From this massive repository of data, we are able to more effectively diagnose, risk-segment, and treat cancer patients. At the same time, the portfolio of therapeutics continues to grow at an unprecedented pace; in 2022, the FDA approved 13 new agents for the care of patients with oncologic and hematological diseases.2 In the aggregate, the US system of innovation creation and care delivery is achieving the highest aggregate sur- rate in the world, resulting in more than 18 million cancer survivors in the United States alone.3 In a recent Washington Post opinion piece, David Goldhill made the plausible argument that a system like ours that competes to deliver the greatest level of innova- tion to patients provides profound benefits world- wide by advancing emerging surgical and cancer therapeutic technologies. The result is a life-dividend that is measured in millions of lives saved.

Yet in a time of such wonders there is cause for concern: This pace of innovation has come at a For the total cancer care expenditures in the United States now exceed $156 billion, with patients and their families directly shouldering over $16 billion in out-of-pocket costs annually.4 In light of the rapid growth in health care costs and patient-borne cost-sharing, we are facing a potential breaking point. As policy makers, payers, and state and federal health care administrators focus increasingly on controlling costs, pressures are growing on physicians, health systems, and innovation leaders to do more with less. Toward that end, physicians face continued cuts to the Medicare Physician Fee Schedule, systems face de facto cuts (once inflation is factored in) to both outpatient and inpatient reimbursement, and the focus of legisla- tors and administrators is on continuing to bend the cost curve, come hell or high water.

Initiatives like shifting toward value-based care payments and growing calls for greater price trans- parency represent well-intentioned forays toward efficiency through strangulation can undermine the best capacities of our current cancer care system. We should commit to more careful definitions of what represents high value for cancer patients and their families and develop transparent economic systems that incentivize better stewardship of resources within our system. We should also avoid making the false choice of cost containment but risk being willfully blind to the fact that reducing costs without reducing

the value of care for vulnerable cancer patients is harder than it seems. “Value” remains a poorly defined word in most policy edicts and our system suffers because of the resulting lack of clarity and specificity. Brute-force methods that may produce effective cost containment in the domain of primary care (capitated payments, narrow networks, shifts toward care in less intensive settings, and greater reliance on non-physician providers) may be a poor fit for a cancer care innovation delivery model that relies increasingly on interpretation of complex genomic testing data, navigation of a complex portfolio of targeted therapeutics, integration of hundreds of advanced therapeutic interventional trials, and effective management of the emotional dimensions of caring for patients with a potentially life-ending illness.

So how do we begin? I think we need to come to the realization that less is not always more and that models that seek efficiency through strangulation can undermine the best capacities of our current cancer care system. We should commit to more careful definitions of what represents high value for cancer patients and their families and develop transparent economic systems that incentivize better stewardship of care delivery within that model. We should also avoid making the false choice of undervaluing innovation. To embrace a mindset of scarcity at a time of profound patient need would be reckless. Sometimes the best way forward is to pause, think, and then resume with deeper understand- ing of where to go next.

Joseph Alvarnas, MD

EDITORS

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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REFERENCES


Joseph Alvarnas, MD

EDITOR-IN-CHIEF

FROM THE EDITOR-IN-CHIEF
IKEMA (N=329) included dyspnea, cough, nasal congestion, and nausea. Anaphylactic episodes, and the day after in 24% of episodes. Of those experiencing an infusion-related reaction experienced it during the first cycle occurred on the infusion day in 99% of episodes. In patients treated with Isa-Kd, 95% infusion and resolved on the same day in 98% of the cases.

Based on ICARIA-MM, IRRs occurred in 38% of patients treated with SARCLISA, WARNINGS AND PRECAUTIONS

CONTRAINDICATIONS

IMPORTANT SAFETY INFORMATION

SARCLISA (isatuximab-irfc) is indicated:

INDICATION

In combination with pomalidomide and dexamethasone (1-3 prior therapies) in patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor.

In combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy.

The most common (≥21%) second primary malignancies in ICARMA-MM and IKEMA (N=330) 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 completed treatment after resection of the skin cancer.

Monitor patients for the development of second primary malignancies.

Laboratory Test Interference

SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false-negative indirect antiglobulin (IA) test. The incidence of indirect antiglobulin test was positive during Isa-Pd treatment in 68% of the tested patients, and during Isa-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, it has already started, and 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-cross-matched ABO/Rh-compatible RBCs can be given as per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

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

Embryo-Fetal Toxicity

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

ADVERSE REACTIONS

In combination with pomalidomide and dexamethasone: The most common adverse reactions (≥20%) were upper respiratory tract infections, pneumonia and diarrhea. The most common hematologic laboratory abnormalities (≥200%) were decreased hemoglobin, decreased neutrophils, decreased lymphocytes, and decreased platelets.

In combination with carfilzomib and dexamethasone: The most common adverse reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, fatigue, hypertension, diarrhea, pneumonia, dyspnea, insomina, bronchitis, cough, and back pain. The most common hematologic laboratory abnormalities (≥200%) were decreased hemoglobin, decreased lymphocytes, and decreased platelets.

Serious adverse reactions occurred in 62% of patients receiving Isa-Pd. Serious adverse reactions in ≥1% of patients included pneumonia and infections (fatigue, hypotension, diarrhea, pneumonia, dyspnea, insomnia, bronchitis, cough, and back pain). Serious adverse reactions in ≥1% of patients were pneumonia and other infections (fatigue, hypotension, diarrhea).

Serious adverse reactions occurred in 59% of patients receiving Isa-Kd. The most frequent serious adverse reactions in ≥1% of patients who received Isa-Kd were pneumonia (25%) and upper respiratory tract infections (7%). Fatal 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 ≥1% of patients who received Isa-Kd were pneumonia (25%) and upper respiratory tract infections (7%).

Use in Special Populations

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

Please see Brief Summary of the Prescribing Information on the following pages.
Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade ≥2 reactions, interrupt SARCLISA infusion and provide appropriate medical management. For patients with grade 2 or grade 3 reactions, if symptoms improve to grade 1 or lower, restart SARCLISA infusion at half the initial infusion rate, with support 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 immediately if necessary. If grade 2 or grade 3 infusion-related reactions are not prevented, see “Doseage and Administration (2.4)“; in case symptoms do not improve, grade 1 interruption of SARCLISA infusion, persist or worsen despite appropriate medications, or require hospitalization, permanently discontinue SARCLISA administration. Patients may discontinue SARCLISA if an anaphylactic reaction or life-threatening (grade 4) infusion-related reaction occurs and institute appropriate management.

SARCLISA may cause neutropenia.

In patients treated with Isa-Kd, neutropenia occurred in 96% of patients and grade 3–4 neutropenia occurred in 86% of patients. Neutropenic complications occurred in 30% of patients, including febrile neutropenia (12%) and neutropenic infections (23%). SARCLISA-related grade 3 or grade 4 neutropenic complications occurred in 21% of patients, including grade 3 neutropenia in 13% of patients and grade 4 neutropenia in 8% of patients.

Complete blood cell counts periodically during treatment. Consider the use of antibiotics and antifungal prophylaxis during treatment. SARCLISA should be used with caution in patients with neutropenia for signs of infection. In a case of grade 4 neutropenia delay sarclisa until neutrophil count recovery to at least 1.5 x 10⁹/L, and provide supportive care with granulocyte colony-stimulating factor. Follow institutional, according to institutional guidelines, dose reductions of SARCLISA are recommended.

6.3 Secondary Malignancies

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

In IPA-MM, secondary primary malignancies occurred in 0.5% of patients (3% of patients in the Isa-Kd arm) and in 0.7% of patients in the Isa-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 Isa-Pd arm.

The most common (≥5%) secondary primary malignancies in ICA-MMM and IMM (N=329) included skin cancers (4% with Isa-Pd) and myeloma (1% with Isa-Pd). SARCLISA-containing regimens and 1.5% with comparator regimens. Patients with skin cancer continued treatment with SARCLISA for the development of secondary primary malignancies.

6.4 Laboratory Test Interferences

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Immunochemical measurement of immunoglobulins and Bence Jones proteins may be carried out following SARCLISA infusion. Patients treated on both serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous Myeloma. This interference can impact the accuracy of immunofixation assay. All patients with multiple myeloma and Bence Jones protein elevation should be questioned further. Serum protein electrophoresis and immunofixation tests should be performed before and after SARCLISA administration.

6.5 Embryo-Fetal Toxicity

SARCLISA should not be given to women of childbearing potential and proper contraceptive precautions should be taken. Women of childbearing potential who are also infertile should not breastfeed. When SARCLISA is administered during pregnancy, the potential risk to the fetus should be considered. Women should use effective contraception during treatment and for 5 months after the last dose. Patients should be advised to use effective contraception (see Warnings and Precautions (5.1)“.

6.6 Clinical Trial Experience

Because clinical trials are conducted under very varying, adverse conditions, observed results of the clinical trials do not necessarily directly compare to the results of clinical trials of another drug and may not reflect the rates observed in practice. SARCLISA may cause fetal cell death and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise women to avoid breast feeding. Inform patients of the potential risk of fetal harm and advise women of reproductive potential to avoid pregnancy during treatment. SARCLISA was not studied in pregnancy. The use of condoms is not known to prevent transmission of SARCLISA to neonates and infants exposed to SARCLISA in utero until a hematology evaluation is completed.

6.7 Adverse Reactions

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

• Infusion-Related Reactions (2.1)“.

• Neutropenia (see Warnings and Precautions (5.2)“.

• Second Primary Malignancies (6.3)

• Pneumonia (see Warnings and Precautions (5.4)“.

Table 3 describes the adverse reactions in IA/MM.

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)“.

4.1 Hematologic

4.2 Renal and Hepatic

4.3 Gastrointestinal

4.4 Respiratory, Thoracic and Mediastinal

4.5 Blood and Lymphatic System

4.6 Infections

4.7 Gastrointestinal Disorders

4.8 Respiratory, Thoracic and Mediastinal Disorders

4.9 Blood and Lymphatic System Disorders

4.10 Infections

The most common symptoms (≥5%) of an infusion-related reaction in ICA-MM and IMM (N=329) included dyspnea, cough, nasal congestion, and nausea. Anaphylactic reactions occurred in less than 1% of patients.

To decrease the risk of severe infusion-related reactions, predmedicate patients prior to SARCLISA infusion with acetylcysteine, H2 antagonists, diphenhydramine, or equivalent, and desmopressin (see Doseage and Administration (2.2)).
The recommended dose of SARCLISA is 10 mg/kg actual body weight administered as an intravenous infusion in combination with pomalidomide and before SARCLISA and carfilzomib administration.

Administer the recommended premedication agents 15 to 60 minutes prior to starting a SARCLISA infusion. Serious adverse reactions requiring hospitalization or death occurred in 6% of patients who received SARCLISA. Some of the serious adverse reactions in ≥5% of patients who received SARCLISA were pneumonia (16%), and upper respiratory tract infections (9%). Adverse reactions with a fatal outcome during treatment were reported in 3% of patients in the Isa-Kd group (those occurring in more than one patient) were pneumonia occurring in 1% and cardiac failure in 1% of patients. Permanent treatment discontinuation due to an adverse reaction (grades 3–4) occurred in 8% of patients who received SARCLISA. The most frequent adverse reactions reporting permanent discontinuation in patients who received SARCLISA were infections (28%). SARCLISA alone was discontinued in 35% of patients due to infusion-related reactions. Dosage interruptions due to adverse reactions occurred in 33% of patients who received SARCLISA. The most frequent adverse reaction requiring dosage interruption was infusion reaction (30%).

The most common adverse reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, fatigue, hypertension, diarrhea, dermatitis, bruising, cough, and back pain. Table 5 summarizes the adverse reactions in IEMKA.

### Table 5: Adverse Reactions (≥10%) in Patients Receiving SARCLISA, Carfilzomib, and Dexamethasone with a Difference Between Arms (% Compared to Control Arm in IEMKA)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SARCLISA + Carfilzomib + Dexamethasone (Isa-Kd)</th>
<th>Carfilzomib + Dexamethasone (Kd)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-related reaction</td>
<td>49.6</td>
<td>40.6</td>
<td>3.3</td>
<td>0.0</td>
<td></td>
<td>49.6</td>
<td>40.6</td>
<td>3.3</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>42.5</td>
<td>32.3</td>
<td>0.0</td>
<td>0.3</td>
<td></td>
<td>42.5</td>
<td>32.3</td>
<td>0.0</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>97</td>
<td>57</td>
<td>0</td>
<td></td>
<td></td>
<td>97</td>
<td>57</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>102</td>
<td>38.4</td>
<td>30</td>
<td>15.5</td>
<td></td>
<td>102</td>
<td>38.4</td>
<td>30</td>
<td>15.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>24.3</td>
<td>23.3</td>
<td>0.0</td>
<td>0.8</td>
<td></td>
<td>24.3</td>
<td>23.3</td>
<td>0.0</td>
<td>0.8</td>
<td></td>
<td></td>
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<tr>
<td>Vascular disorders</td>
<td>23</td>
<td>15.0</td>
<td>0</td>
<td></td>
<td></td>
<td>23</td>
<td>15.0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>37</td>
<td>20.6</td>
<td>0.0</td>
<td>1.8</td>
<td></td>
<td>37</td>
<td>20.6</td>
<td>0.0</td>
<td>1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>29</td>
<td>24.0</td>
<td>0</td>
<td></td>
<td></td>
<td>29</td>
<td>24.0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>29</td>
<td>24.0</td>
<td>0</td>
<td></td>
<td></td>
<td>29</td>
<td>24.0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>10</td>
<td>15.0</td>
<td>0</td>
<td></td>
<td></td>
<td>10</td>
<td>15.0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrintestinal disorders</td>
<td>150</td>
<td>150</td>
<td>0</td>
<td></td>
<td></td>
<td>150</td>
<td>150</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>36</td>
<td>28.0</td>
<td>2.5</td>
<td>0.0</td>
<td></td>
<td>36</td>
<td>28.0</td>
<td>2.5</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14</td>
<td>15.0</td>
<td>0.0</td>
<td></td>
<td></td>
<td>14</td>
<td>15.0</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>55</td>
<td>47.0</td>
<td>0</td>
<td></td>
<td></td>
<td>55</td>
<td>47.0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 6: Hematology Laboratory Abnormalities During the Treatment Period in Patients Receiving Isa-Pd versus Pd in IEMKA

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)</th>
<th>Pomalidomide + Dexamethasone (Pd) (N=149)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin decreased</td>
<td>96</td>
<td>32.0</td>
<td>0</td>
<td>97</td>
<td>28</td>
<td>0</td>
<td>96</td>
<td>32</td>
<td>0</td>
<td>97</td>
<td>28</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>96</td>
<td>24.0</td>
<td>61</td>
<td>38</td>
<td>31</td>
<td>96</td>
<td>24.0</td>
<td>61</td>
<td>38</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>92</td>
<td>42.0</td>
<td>13</td>
<td>92</td>
<td>35</td>
<td>8</td>
<td>92</td>
<td>42</td>
<td>13</td>
<td>92</td>
<td>35</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>84</td>
<td>14.0</td>
<td>16</td>
<td>79</td>
<td>9</td>
<td>15</td>
<td>84</td>
<td>14</td>
<td>16</td>
<td>79</td>
<td>9</td>
</tr>
</tbody>
</table>

The denominator used to calculate the percentages was based on the safety population.
Payment Models

DOES THE ENHANCING ONCOLOGY MODEL (EOM), proposed as the successor to Medicare’s first alternative payment model in cancer care, have enough incentives to draw small practices into value-based care? Or will this new model, which draws on the Oncology Care Model (OCM), scare off practices that would prefer an on-ramp before facing 2-sided risk?

On November 1, 2022, The American Journal of Managed Care® (AJMC®) welcomed 4 experts to its headquarters in Cranbury, New Jersey, for a Stakeholders’ Summit: Putting the Enhancing Oncology Model Into Practice. As the Center for Medicare and Medicaid Innovation (CMMI) reviews applications from practices that would like to start the model on July 1, 2023, AJMC® sought to hear from oncology leaders with direct experience in implementing both the OCM and commercial value-based models in community practices.

STUART STAGGS, MSIE, senior director for strategic programs, The US Oncology Network, served as moderator for the discussion, which featured these panelists:

- STEPHEN M. SCHLEICHER, MD, MBA, chief medical officer of Tennessee Oncology, a part of the OneOncology network;
- KASHYAP PATEL, MD, CEO of Carolina Blood and Cancer Care Associates and president of the Community Oncology Alliance (COA); and
- STEPHEN “FRED” DIVERS, MD, chief medical officer of the American Oncology Network (AON) and a medical oncologist at Genesis Cancer and Blood Institute of Arkansas.

Staggs started the discussion by revisiting the OCM, which began in 2016 and ended on June 30, 2022, having been extended for 1 year due to the COVID-19 pandemic. Under the model, practices were evaluated in 6-month performance periods, based on their ability to perform well on quality measures and save Medicare money. Evaluations that looked at early performance periods found that the OCM did not save money, but as the experts taking part in the AJMC® discussion noted, that finding was not uniform—some practices mastered the model and saved more money as they went along.

To help practices implement practice transformation steps—such as patient navigation, 24/7 access to medical records, and technology innovations to schedule same-day appointments—practices received payments of $160 per patient per month during treatment. Payments for Monthly Enhanced Oncology Services (MEOS) will be cut to $70 under the EOM, with an extra $30 for patients who also receive Medicaid. The extra $30 does not count toward a patient’s total cost of care.

Staggs asked how practices might have reacted if CMMI had not offered a successor to the OCM.

“The OCM was a first blueprint, an architectural drawing of translating the concept of the CMMI model into real action,” Patel said. Practices invested in the model, hiring staff and making other changes, “in good faith” to enhance the patient experience and reduce the cost of care. The EOM is not perfect, but without something like it, “practices would have been disappointed,” he said.

Schleicher agreed, calling the OCM “a very useful pilot” that offered resources to practices so they could invest in transformation. He emphasized that some practices were quite successful even if overall evaluations found that the OCM did not save money—and added that from a quality perspective, the difference was huge. “It would be very detrimental not to continue this momentum that our practices [in OneOncology] and many others have had,” he said.

“One of the keys of the OCM and EOM is really trying to keep the patient at the center of the equation,” Divers said. In practices that used the resources to create additional patient touchpoints, patient experience has dramatically improved. “We obviously didn’t want to see that go away,” he said, and AON practices are working to keep the additional staffing in place, despite the yearlong gap between models without the MEOS payments.

Staggs asked what it was like to work with CMMI over the years that the OCM was in place, compared with the relative surprise that EOM represented. Divers said the EOM did come “out of the blue,” and practices await specifics on reporting requirements. Schleicher and Patel agreed, but they noted the competing priorities at CMS; they remain hopeful that there will be opportunities to make changes over time, as was the case with the OCM.

The goal, Divers said, should be to get the right therapy for the patient. Practices will find value in the EOM if it generates data that can be used with an electronic health record to help practices match each patient with the right treatment protocol. “You can’t strictly focus on the cost aspect,” he said.

Limited to 7 Cancer Types

A major change from the OCM is that the new model will cover Medicare patients receiving systemic chemotherapy (meaning those receiving only hormonal therapy are excluded) for 7 cancer types: breast cancer, chronic leukemia, small intestine/colorectal cancer, lung cancer, lymphoma, multiple myeloma, and prostate cancer. This will limit the number of patients covered under the EOM, thus limiting those eligible for MEOS payments. With the MEOS payments themselves trimmed as well, practices will have less money to cover added services, even though practices will likely extend those services to all patients.

The shift has its pluses and minutes, the panelists agreed.

“We can narrow our focus,” Divers said. Benchmarking should be easier for CMMI, “so we can really nail down what the cost of care might be for these tumor types.”

Compared with the OCM, Divers said, the EOM will incorporate more detail about cancer staging and features, so benchmarks and pricing in the EOM should be more accurate. But the question of whether the number of patients covered will be enough to qualify for an Advanced Alternative Payment Model remains to be seen.

“On the plus side, I agree with predictability,” Schleicher said, both from a cost and an accountability standpoint. The question is whether the dramatic cut to MEOS payments and the other shifts in the financial model allow practices to effectively manage high-risk patients, including treatment and palliative care.

Because practices are asked to track social determinants of health (SDOH) and address health equity, not having MEOS payments for all patients is a challenge. “It would have been nice to have everybody still in the model,” Schleicher said, “because quality metrics are going to be important.”

“I hope we don’t see a negative impact by not including those [with] early-stage [disease],” Divers added, which could mean fewer touch points and poorer compliance. “It may turn into more advanced disease.”
Making the EOM a “Win”
Staggs asked whether oncologists could combine the EOM with other models within CMMI, such as chronic care management, which could allow them to capture revenue to replace what is being lost in the switch from the OCM to the EOM’s smaller MEOS payments.

Patel sees potential to combine the programs, given that both contribute to reduced per-member per-month spending for Medicare and reduced hospital admissions. “It may help practices to have a little more of a revenue stream to justify a more broad-based approach,” he said.

CMMI had to design a program that was “a win” from a financial perspective. Divers said. “And if you took the MEOS out in OCM, it was a win.”

The challenge is that practices are now asked to do more data collection with less guaranteed revenue and to still meet the new goals of health equity and electronic patient-reported outcomes. Divers noted that CMMI has not offered clear instructions on how to do this; it appears practices can select a vendor of their choosing. Adding this process should be comparatively easy for larger practices, but it is unclear how it will be possible for smaller practices that want to participate.

Schleicher concurred. “We need the data, and we need to learn a lot of these things,” he said, explaining that he is concerned about attracting those practices that have not yet tried value-based care, specifically the OCM. Among the potential roadblocks are the smaller MEOS payments, new reporting requirements, and requirement for 2-sided risk from the start of the model.

“My concern is the selection bias,” Schleicher said; in other words, he fears the model will only attract those practices with prior experience in value-based care, and no new data will be collected from practices that did not try the OCM.

“I’ve already learned how to report in the OCM,” he continued. While new reporting requirements will add important information, they also put new burdens on practices—and that’s a concern for practices that have not yet built a reporting infrastructure.

Addressing Health Equity
Tackling health equity is not a small issue, and “it’s been an issue for a long time,” Staggs said. “What do practices do about that? How do they partner? How do they get started?”

Patel, who has made health equity a centerpiece of his tenure as COA president, said his small oncology practice in South Carolina has set up a program to find resources to improve access for patients who lack financial means for coverage or cost-sharing. The COVID-19 pandemic has increased the need for such measures, he said.

Although improving health equity is a goal of EOM, Patel said, “CMMI has not specified how they’re going to reward practices for addressing that.”

In his own practice, when he set up a program to screen patients for SDOH, he learned that 3 patients were homeless and found them shelter. But providing such assistance “takes a lot of time and resources,” Patel said, and he is trying now to work with CMMI to create rewards within the model for practices that help patients, “so that [those practices] don’t feel that the model is failing for them.”

Ideally, Divers said, CMMI can aggregate data generated through the EOM that will indicate practices where dollars are best spent to make a difference. Some practices have connections with charitable resources to provide patients with food or with gas cards for transportation, but not all do.

Schleicher said community partnerships can work wonders in this area, but they take time to establish. “These do take infrastructure to build, and then to report on it and learn about—so it’s not an easy fix,” he said.

The SDOH focus is an outgrowth of lessons from OCM, Schleicher explained, as practices took responsibility and created structures for keeping patients out of the emergency department (ED) and the hospital.

“I worry that we’re going to continue to learn from a selection bias group of practices that have done well and have invested in this and are confident enough that they can do well...vs the broader population of cancer care practices that would love to rise up and also get involved.”

—Stephen M. Schleicher, MD, MBA, chief medical officer, Tennessee Oncology

Smaller MEOS Payments
The panel highlighted how the reduced MEOS payments in the EOM are offset by at least 2 positives: (1) a $30 monthly payment for patients who are eligible for Medicaid, which does not count toward the total cost of care; and (2) the elimination of patient cost-sharing for EOM services, which providers say will encourage advanced care planning.

Schleicher said the list of minuses related to the MEOS changes “is longer,” starting with the fact that reduced revenue comes alongside increased reporting demands. Once again, he emphasized how the combined effect of the financial pieces will drive who signs up for the model. “I worry that we’re going to continue to learn from a selection bias group of practices that have done well and invested in this and are confident enough that they can do well... vs the broader population of cancer care practices [that] would love to rise up and also get involved,” Schleicher said. “What’s the barrier to entry?”

What About Small Practices?
As Staggs pointed out, not every practice has the size and breadth of Schleicher’s Tennessee Oncology or of Texas Oncology, a practice in The US Oncology Network. How does a small practice that wants to pursue the EOM, or value-based care generally, take the first step?

“Don’t try to go it alone,” Schleicher advised. “There are a lot of people to learn from,” including leaders within COA. For his part, Patel said small practices should focus squarely on keeping patients out of the hospital or the ED, not only for cost reasons but also because that is where they can make a significant difference in quality of life.

Practices will definitely need help if they are expected to take on 2-sided risk from the outset, which is another key departure from the OCM. Under the EOM, there are 2 risk levels, with the lower-risk option still requiring practices to report under the Merit-based Incentive Payment System.

Divers said he doesn’t have a problem with asking practices to have some “skin in the game,” and Schleicher agreed to a point—but he worries what will happen if there are problems with the model as it gets up and running, especially for the practices that have no experience from the OCM. Having 2-sided risk “from the start gives me [pause],” he said, adding that practices with no OCM experience should approach the EOM with “a little bit of caution,” he said.

Staggs asked if the EOM option that allows practices to pool data, to compare prior performance periods and savings, offers a solution.

“I don’t know the answer,” Schleicher said. Pooling is being discussed to improve case mix, which in theory could help smaller practices. For large practices that did well under the OCM, there are concerns that performance be measured against prior results, comparisons will still be somewhat against prior results, and it will be hard to continue to find savings. But pooling can also affect an oncology group’s baseline measures, Schleicher said, and so far, there aren’t enough details available for oncology groups to map out whether pooling makes financial sense.

Remove Drug Costs From the Equation
Staggs asked each panelist: If you could change 1 financial element about the EOM, what would it be?

Patel spoke about a trend he’s seeing in his practice. “The biggest unknown is the impact of chronic COVID long-haulers,” he said. “Data are emerging that nationally, 20% of patients will become long-haulers, and this will (mean) more spending, because these patients may be sicker. I have patients who had stable [chronic lymphocytic leukemia], but now they have [atrial fibrillation] because of COVID. [Others] may have thrombophilia...it’s (certainly) going to raise the cost of care.” CMMI must add a risk adjustment that factors long-term effects of COVID into the total cost of care, he said.

For Divers, the reduced MEOS payments are a concern, particularly when it comes to enticing more practices to try a value-based model. “When I think about how you change behavior, economically, you need something to get to get the ball rolling,” he said. “I’m not sure that this MEOS [level] is enough to bring everybody to the table.”

He suggested that CMMI look for creative solutions to tie additional revenue to the back end of performance, based on practices’ data. »
PAYMENT MODELS

Schleicher agreed. Between the rate cut and the population changes, practices will end up with about a quarter of the MLOS payments, “but we still deliver the same care.

“That’s a little tough, especially for groups that haven’t done it yet,” Schleicher said. Complicating matters is that if practices take on more risk under the EOM, newly approved drugs that aren’t yet recognized under the model will, for at least 6 months, be prescribed at an even deeper penalty, with fewer MLOS dollars to offset this cost.

“If there was a way for the appropriate drugs to just not be a part of this, which is easier said than done, then the focus really becomes on the things we can control, like better management of [adverse] effects, better palliative care, better end-of-life care,” and other things that affect patient experience. “It allows you to focus a lot more on those and take out the uncontrollable piece.”

Advances in cancer therapies have offered the greatest improvements in survival, Divers said, but financial models haven’t always kept pace. “You don’t ever want to put a provider—either in your own practice, or in any network—in the position of saying, because of a financial model, ‘I’m being forced from a [economic] perspective, from [the] administration or the government, to... withhold care,’” he said.

“What we ought to understand is that if you have a patient at the center of this model, the most benefit to the patient will come from what you just said: Keep drugs out of the equation,” Patel agreed. This will reduce hospitalization, keep patients out of the ED, help patients get back to work, improve their quality of life, and reduce the cost of care, he said.

“I don’t think any of us would ever withhold care, but it’s still where this [model] is,” Schleicher said.

“It takes away the ability to really focus on the things we can control and [to put the] patient first.”

FROM OUR PARTNERS

MA Beneficiaries May Be at Disadvantage for Complex Cancer Surgeries

Hayden E. Klein

PATIENTS WITH CANCER enrolled in Medicare Advantage (MA) are more likely to go to hospitals with physicians less experienced at performing complicated surgeries compared with patients with cancer enrolled in traditional Medicare, according to an analysis by a team from City of Hope, the National Cancer Institute–certified Comprehensive Cancer Center based in Duarte, California.

The investigators also found these patients were more likely to die within 30 days after removal of their liver, pancreas, or stomach.

These findings were included in the study “Medicare Advantage: A Disadvantage for Complex Cancer Surgery Patients,” published in the Journal of Clinical Oncology.

To arrive at these findings, the study authors looked at the data of 7,6,655 Medicare beneficiaries. The median age was 74 and was made up of 51% women and 39% MA beneficiaries. Their analysis included 31,913 colectomies, 10,358 proctectomies, 4604 hepatectomies, 2895 pancreatectomies, 3639 gastrectomies, 1555 esophagectomies, and 21,691 lung resections.

The authors found that beneficiaries were less likely to receive care at a high-volume hospital, except when undergoing colectomies.

Compared with traditional Medicare beneficiaries, mortality was significantly higher among MA beneficiaries undergoing:

- gastrectomy (adjusted risk difference [ARD], 1.5%; 95% CI, 0.01-2.9; P = .036)
- pancreatectomy (ARD, 2.0%; 95% CI, 0.80-3.3; P = .002)
- hepatectomy (ARD, 1.4%; 95% CI, 0.1-2.9; P = .04)

Patients with cancer enrolled in MA were 1.5 times more likely to die within 1 month after surgical removal of their stomach or liver, and twice as likely to die within 1 month after oncologic surgery of the pancreas, compared with patients with traditional Medicare.

However, the authors also found MA beneficiaries incurred lower estimated hospital costs compared with traditional Medicare beneficiaries.

Of an estimated 29 million Americans enrolled in Medicare, nearly half are enrolled in MA plans. Additionally, of the 6.6 million Medicare-eligible Californians, 47% are enrolled in MA plans.

A main difference is patients enrolled in Medicare can visit any doctor or hospital in the United States that accepts Medicare. However, in most cases, MA beneficiaries can only visit doctors and providers in the plan’s network and service area.

According to Joseph Alvarnas, MD, vice president for government affairs at City of Hope, this study—which he was not involved in—shows too many Medicare Advantage beneficiaries lack access to optimal cancer care and therefore suffer adverse outcomes.

“As of end of this current enrollment period, 50% of Medicare beneficiaries will likely enroll in Medicare Advantage plans,” he said in a statement from the City of Hope. “While these plans can provide patients with some added benefits, a significant missed opportunity exists in the narrow network design that many of these plans utilize. Access to high expertise cancer care, including surgical care, produces better outcomes for patients.”

Alvarnas is the editor in chief of Evidence-Based Oncology™.

“The study suggests that cancer patients with Medicare Advantage would experience better short-term health outcomes if more of them had access to hospitals that frequently perform complex cancer surgery,” said Mustafa Raoof, MD, MS, surgical oncologist at City of Hope and lead author of the study. “Research has repeatedly linked improved surgical outcomes to cancer patients who receive care at a National Cancer Institute–designated cancer center, such as City of Hope, or at hospitals with high surgery volumes or that are accredited by the Commission on Cancer.”

Patients with traditional Medicare compared with MA were more likely to be treated at a teaching hospital (23% vs 8%), a hospital accredited by the Commission on Cancer (57% vs 33%), or a National Cancer Institute-designated cancer center (15% vs 3%).

Further, Medicare beneficiaries were more likely to be treated at hospitals with a higher median number of total beds, intensive care unit beds, operating rooms, and annual inpatient surgical volume.

However, MA beneficiaries experienced delays of more than 2 weeks from diagnosis to first course of therapy.

“A reason for the delay could be the required prior authorization that Medicare Advantage beneficiaries with an HMO have to undergo,” City of Hope said. “While this referral process is intended to limit unnecessary medical care, it can cause delays for Medicare Advantage beneficiaries who need specialized services, such as complex cancer surgery.”

REFERENCES


BESREMi targets the bone marrow, the source of PV, so you can address the underlying disease.

**INDICATION**

BESREMi is indicated for the treatment of adults with polycythemia vera.

**IMPORTANT SAFETY INFORMATION**

**WARNING: RISK OF SERIOUS DISORDERS**

Interferon alfa products may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping therapy.

**CONTRAINDICATIONS**

- Existence of, or history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt.
- Hypersensitivity to interferons including interferon alfa-2b or any of the inactive ingredients of BESREMi.
- Moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.
- History or presence of active serious or untreated autoimmune disease.
- Immunosuppressed transplant recipients.

**WARNINGS AND PRECAUTIONS**

Patients exhibiting the following events should be closely monitored and may require dose reduction or discontinuation of therapy:

- Depression and Suicide: Monitor closely for symptoms and need for treatment.
- Endocrine Toxicity: Discontinue if endocrine disorders occur that cannot be medically managed.
- Cardiovascular Toxicity: Avoid use in patients with severe, acute or unstable cardiovascular disease. Monitor patients with history of cardiovascular disorders more frequently.
- Decreased Peripheral Blood Counts: Perform blood counts at baseline, every 2 weeks during titration, and at least every 3-6 months during maintenance treatment.
- Hypersensitivity Reactions: Stop treatment and immediately manage reaction.
- Pancreatitis: Consider discontinuation if confirmed pancreatitis.
- Colitis: Discontinue if signs or symptoms of colitis.
- Pulmonary Toxicity: Discontinue if pulmonary infiltrates or pulmonary function impairment.
- Ophthalmologic Toxicity: Advise patients to have eye examinations before and during treatment. Evaluate eye symptoms promptly and discontinue if new or worsening eye disorders.
- Hyperlipidemia: Monitor serum triglycerides before BESREMi treatment and intermittently during therapy and manage when elevated.

**ADVERSE REACTIONS**

The most common adverse reactions reported in > 40% of patients in the PEGINVERA study (n=51) were influenza-like illness, arthralgia, fatigue, pruritis, nasopharyngitis, and musculoskeletal pain. In the pooled safety population (n=178), the most common adverse reactions greater than 10%, were liver enzyme elevations (20%), leukopenia (20%), thrombocytopenia (19%), arthralgia (13%), fatigue (12%), myalgia (11%), and influenza-like illness (11%).

**DRUG INTERACTIONS**

Patients on BESREMi who are receiving concomitant drugs which are CYP450 substrates with a narrow therapeutic index should be monitored to inform the need for dosage modification for these concomitant drugs. Avoid use with myelosuppressive agents and monitor patients receiving the combination for effects of excessive myelosuppression. Avoid use with narcotics, hypnotics or sedatives and monitor patients receiving the combination for effects of excessive CNS toxicity.

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.
- Lactation: Advise women not to breastfeed during treatment and for 8 weeks after the final dose.
- Avoid use in patients with eGFR <30 mL/min.

Please see Brief Summary of full Prescribing Information, including Boxed Warning, on adjacent pages.

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Risk of Serious Disorders
Interferon alfa products may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persisting or increasing signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping therapy (see Warnings and Precautions [5.1, 5.2, 5.3, 5.4] and Adverse Reactions [6.1]).

1 INDICATIONS AND USAGE
BESREMi is indicated for the treatment of adults with polycythemia vera.

2 CONTRAINDICATIONS
BESREMi is contraindicated in patients with:
• History of, or evidence of, severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt
• History of severe or unstable cardiovascular disease, (e.g., uncontrolled hypertension, congestive heart failure.
• History of or active untreated autoimmune disease

5 WARNINGS AND PRECAUTIONS
5.1 Depression and Suicide
Life-threatening or fatal neuropsychiatric reactions have occurred in patients receiving interferon alfa products, including BESREMi. These reactions may occur in patients with and without previous psychiatric illness. Serious neuropsychiatric reactions have been observed in 3% of patients treated with BESREMi during the clinical development program. Among the 176 patients in the clinical development program of BESREMi, 17 cases of depression, depressive symptoms, depressed mood, and listlessness occurred. Of these seventeen cases, 3.4% of the patients recovered with temporary drug interruption and 2.8% stopped BESREMi treatment. Other central nervous system effects, including suicidal ideation, attempted suicide, aggression, bipolar disorder, mania and confusion have been observed with other interferon alfa products. BESREMi is contraindicated in patients with a history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt (see Contraindications [4]).

Closely monitor patients for any symptoms of psychiatric disorders and consider psychiatric consultation and treatment if such symptoms emerge. If psychiatric symptoms worsen, it is recommended to discontinue BESREMi therapy.

5.2 Endocrine Toxicity
Endocrine toxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include worsening hypothyroidism and hyperthyroidism. Autoimmune thyroiditis and other thyroid toxicities may include worsening hypothyroidism and hyperthyroidism. Autoimmune thyroiditis may occur in patients with and without previous psychiatric illness. BESREMi is contraindicated in patients with autoimmune thyroiditis (see Contraindications [4]).

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
The following clinically significant adverse reactions are described elsewhere in the labeling.

• Depression and Suicide (see Warnings and Precautions [5.1])
• Endocrine Toxicity (see Warnings and Precautions [5.2])
• Ophthalmologic Toxicity (see Warnings and Precautions [5.10])

7 DRUG INTERACTIONS

8 ADVERSE REACTIONS

9.1 Hepatotoxicity
Hepatotoxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include increases in serum ALT, AST, GGT and bilirubin. BESREMi is contraindicated in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment (see Contraindications [4]).

9.2 Hypersensitivity Reactions
Severe hypersensitivity reactions have occurred in patients receiving interferon alfa products, including BESREMi. These reactions may include angioedema, anaphylaxis, bronchoconstriction, urticaria, and vasculitis. These toxicities may include increases in serum ALT, AST, GGT and bilirubin. BESREMi is contraindicated in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment (see Contraindications [4]).

10.1 Hypersensitivity Reactions
Severe hypersensitivity reactions have occurred in patients receiving interferon alfa products, including BESREMi. These reactions may include angioedema, anaphylaxis, bronchoconstriction, urticaria, and vasculitis. These toxicities may include increases in serum ALT, AST, GGT and bilirubin. BESREMi is contraindicated in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment (see Contraindications [4]).

9.4 Immune Reactions
Hypersensitivity reactions have occurred in patients receiving interferon alfa products, including BESREMi. The estimated background risk of major birth defects and miscarriage for the indicated population is approximately 5% for all gestations. Among 178 patients who received BESREMi, 80% were exposed for 12 months or longer, 63% were exposed for three years or longer, and 53% were exposed for greater than five years. While serious adverse reactions were reported 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. In the pooled safety population described in the Warnings and Precautions section, infection or neutropenia was the most common serious adverse reaction observed in the study (25% included urticarial rash (8%), transient ischemic attack (6%) and depression (4%).

11.1 Hypertension
Hypertension has occurred in patients treated with interferon alfa products, including BESREMi. Hypertension, hyperthyroidism, or dyslipidemia occurred in 3% of patients receiving BESREMi. Monitor blood pressure in patients treated with BESREMi, particularly in those patients with a history of hypertension, polycythemia vera, or diabetes mellitus or hypertension. Evaluate eye symptoms promptly. Discontinue BESREMi in patients who develop new or worsening eye disorders.

5.10 Hypertension
Hypertension has occurred in patients treated with interferon alfa products, including BESREMi. These toxicities may include increases in serum ALT, AST, GGT and bilirubin. BESREMi is contraindicated in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment (see Contraindications [4]).

In the clinical development program of BESREMi, 30 patients (20%) experienced liver enzyme elevations, 33 patients received elevations of 1.75-5X ULN, 53 patients were able to resume BESREMi upon resolution of liver enzyme elevations. Liver enzyme elevations have also been reported in patients after long-term BESREMi therapy.

Monitor liver enzymes and hepatic function at baseline and during BESREMi treatment. Reduce BESREMi dosage by 50 mcg for increased ALT/AST/GGT and hold the dosage at 25 mcg at baseline.

5.11 Heparin
Hepatotoxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include increases in serum ALT, AST, GGT and bilirubin. BESREMi is contraindicated in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment (see Contraindications [4]).

Life-threatening or fatal neuropsychiatric reactions have occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include increases in serum ALT, AST, GGT and bilirubin. BESREMi is contraindicated in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment (see Contraindications [4]).

In the clinical development program of BESREMi, 30 patients (20%) experienced liver enzyme elevations, 33 patients received elevations of 1.75-5X ULN, 53 patients were able to resume BESREMi upon resolution of liver enzyme elevations. Liver enzyme elevations have also been reported in patients after long-term BESREMi therapy.

Monitor liver enzymes and hepatic function at baseline and during BESREMi treatment. Reduce BESREMi dosage by 50 mcg for increased ALT/AST/GGT and hold the dosage at 25 mcg at baseline.

5.12 Renal Toxicity
Renal toxicity occurred in patients receiving interferon alfa products, including BESREMi. During BESREMi therapy, 3.1% of patients were reported to have toxic nephropathy. Monitor serum creatinine at baseline and during therapy. Avoid use of BESREMi in patients with eGFR <30 ml/min/1.73m2. BESREMi is contraindicated in patients if severe renal impairment develops during treatment (see Use in Specific Populations [8.6]).

5.13 Dental and Periodontal Toxicity
Dental and periodontal toxicities may occur in patients receiving interferon alfa products, including BESREMi. These toxicities may include dental and periodontal disorders, which may lead to loss of teeth. In addition, mouth dry could have a damaging effect on teeth and oral mucous membranes during long-term treatment with BESREMi. Patients should have good oral hygiene and regular dental examinations.

5.14 Dermatologic Toxicity
Dermatologic toxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include skin rash, pruritus, alopecia, erythema, psoriasis, xeroderma, dermatitis acrocian, hyperpigmentation, oiliness, and hyperhidrosis. Consider discontinuation of BESREMi if clinically significant dermatologic toxicity occurs.

5.15 Driving and Operating Machinery
BESREMi may impact the ability to drive and use machinery. Patients should not drive or use heavy machinery until they know how BESREMi affects their abilities. Patients who experience dizziness, somnolence or hallucinations during BESREMi therapy should avoid driving or using machinery.

5.16 Embryo-Fetal Toxicity
Based on the mechanism of action, BESREMi can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology [12.1] in the full prescribing information and Use in Specific Populations [8.1]). Pregnancy testing is recommended in females of reproductive potential prior to initiating treatment with BESREMi. Advise females of reproductive potential to use an effective method of contraception during treatment with BESREMi and for at least 8 weeks after the final dose (see Dosage and Administration [2.1] in the full prescribing information and Use in Specific Populations [8.1, 8.3]).
Adverse reactions requiring permanent discontinuation in >2% of patients who received BESREMI included depression (8%) arthritis (4%), fatigue (4%), and general physical health deterioration (4%). In the PEGINVERA study, patients were not pre-screened for depression or anxiety disorders.

The most common adverse reactions reported in ≥10% of patients in the PEGINVERA study are listed in Table 2.

Table 2: Adverse Reactions in >10% of Subjects with Polycythemia Vera in the PEGINVERA Study Over 7.5 Years.

<table>
<thead>
<tr>
<th>Adverse Reactions*</th>
<th>BESREMI N=51</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza-like illness</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Local administration site reactions</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Transaminase elevations</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Verrigo</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

*Adverse Reactions defined as all treatment emergent adverse events

5.2 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 in the studies described below with the incidence of antibodies in other studies or to other interferon alfa-2b products may be misleading.

The incidence of binding antibodies to peginterferon alfa-2b-NJFT was 1.4% (21/146) and they were observed as early as 6 weeks post-dosing. Among the patients who tested positive for binding antibodies, none developed neutralizing antibodies.

7 DRUG INTERACTIONS

7.1 Drugs Metabolized by Cytochrome P450

Certain proinflammatory cytokines, including interleukins, can suppress CYP450 enzymes resulting in increased exposures of some CYP substrates. [see Clinical Pharmacology (12.3) in the full prescribing information]. Therefore, patients on BESREMI who are receiving concomitant drugs that are CYP450 substrates with a narrow therapeutic index should be monitored to infer the need for dosage modification for these concomitant drugs.

7.2 Myelosuppressive Agents

Concomitant use of BESREMI and myelosuppressive agents can produce additive myelosuppression. Avoid use and monitor patients receiving the combination for effects of excessive myelosuppression [see Warnings and Precautions (5.4)].

7.3 Narcotics, Hypnotics or Sedatives

Concomitant use of BESREMI and narcotics, hypnotics or sedatives can produce additive neurotoxic psychotropic side effects. Avoid use and monitor patients receiving the combination for effects of excessive CNS toxicity [see Warnings and Precautions (5.1)].
Roy Beveridge, MD, Discusses Pathways, NCCN Guidelines in EGFR Exon 20 Insertion+ NSCLC

ROY BEVERIDGE, MD, based in Louisville, Kentucky, is a senior strategic adviser for Avalere Health and was previously the chief medical officer for Humana. Beveridge spoke with Evidence-Based Oncology (EBO) about the importance of clinical pathways in selecting therapies in non–small cell lung cancer (NSCLC), the use of pathways and guidelines from the National Comprehensive Cancer Network (NCCN), and the emergence of options for EGFR exon 20 insertion–positive NSCLC.

The interview has been edited lightly for clarity.

EBO: Clinical pathways in oncology have been shown to reduce overall costs. Can you share your experience with implementing or using pathway programs in NSCLC as well as any cost-effectiveness data that support this?

BEVERIDGE: Clinical pathways are very important in oncology because they use the best quality of data to make decisions for patients. One is using evidence-based information and inserting that into how one will treat patients with similar characteristics. It's not (only) meant to reduce overall costs, it's (also) meant to create a high level of quality. That usually results in reduction on costs but not always. That's important for [individuals] to recognize. Lung cancer is so complicated that a lot of physicians are unclear on some of the data and don't have the ability to use the best evidence-based medicine at the time that they're seeing a patient during a hectic weekday.

EBO: What's your experience with including genetic testing as part of the pathway?

BEVERIDGE: Genetic testing is hugely important, because the worst thing you can do for a patient is to treat them with a regimen that is clearly going to be ineffective. Unless you do all the genetic testing, and unless you really understand [the] type of cancer the patient has, it's quite possible that you're going to treat someone [with] something that [offers] no benefit. That's the worst-case scenario. Also, you need to know [whether] there's a product out there [that] has meaningful benefit to the patient—you should assess for it. The whole purpose of the war on cancer was to use the right treatment for the right patient.

EBO: What are some of the biggest areas of innovation and market growth as it relates to the diagnosis and treatment of EGFR exon 20 insertion–positive NSCLC?

BEVERIDGE: I look at EGFR exon 20 insertion in NSCLC as part of the whole gamut of how we should be looking at treating [NSCLC]. There are a lot of patients who don't need chemotherapy. There are a lot of patients who need very specific drugs for particular subsets of lung cancer. To be honest, EGFR exon 20 insertion is important, but there is a whole slew of things that one needs to understand with NSCLC so you're choosing the right treatment. If you look at what the choices are, once again, you go back to NCCN pathways, NCCN guidelines—[category] 1A, 2A, whatever you want to choose—but that's what you have to focus on.

EBO: What do you see as some of the biggest areas of innovation in that space?

BEVERIDGE: There are so many new products coming to market so quickly, it's very hard for [individuals] to keep up-to-date. It's very hard for the NCCN guidelines to stay up-to-date. Once again, from a payer's perspective, you need to have a fair arbiter who's looking at the data and looking at the evidence to see whether these usually expensive treatments should be covered. I don't think payers believe they are the experts in all these different types of NSCLCs or cancers by and large. They're looking for key opinion leaders' [KOLs'] thoughts, and they're looking at NCCN placement within pathways.

“I think what payers tend to do is have experts who will be comfortable speaking with the physician and saying, ‘Are you aware of these data?’ It is meant to be a collaborative effort as opposed to ‘Mother may I?’ and people being slapped over the head. That’s not what anyone wants, and it doesn’t help anyone.”

—Roy Beveridge, MD, senior strategic adviser, Avalere Health

EBO: For providers within a plan, how would you keep them abreast of any new updates in clinical practice?

BEVERIDGE: I don't think it's the purview of the payer to educate the physician. I think it's the purview of the payer to say, "Look, the best evidence out there is this. Are you following it? Yes or no? If not, why not?" If part of the answer is, "Well, the physician says I’m not up-to-date," then that's their problem. I think what payers tend to do is have experts who will be comfortable speaking with the physician and saying, "Are you aware of these data?" It is meant to be a collaborative effort as opposed to "Mother, may I?" and people being slapped over the head. That's not what anyone wants, and it doesn't help anyone.

EBO: With NCCN guidelines constantly being updated and new agents coming to market, what are some strategies to ensure that the most appropriate evidence-based guidelines are incorporated into clinical pathway programs?

BEVERIDGE: The practical challenge when one goes to a value-based model is that in cancer, you potentially have an incentive to underutilize treatment for patients. I think this is why the application of up-to-date evidence-based, good pathways like NCCN is so important, because if the economic incentive is not to overprescribe—which is the fee-for-service problem, the value one—there's potentially an incentive to underutilize. The way you've got to choose something [that] is in between is to agree that patients are going to be treated using the best evidence and using pathways that are unassailable.
Alexander Spira, MD, PhD, Discusses Unmet Needs, Treatments for KRAS-Mutated NSCLC

EBO STAFF

Performing next-generation sequencing (NGS) for patients with non–small cell lung cancer (NSCLC) is critical to match them to the right targeted therapy at the right time, especially as new treatment options are being discovered, explained Alexander Spira, MD, PhD, medical oncologist and director of VCS Research Institute & Phase I Trial Program at Virginia Cancer Specialists. Spira spoke with Evidence-Based Oncology® (EBO) earlier this fall. This interview is lightly edited for clarity.

EBO: What unmet needs exist in the treatment of KRAS-positive NSCLC?

SPIRA: We’ve known about KRAS-mutated NSCLC for a long time, and no treatments have worked. Unfortunately, Everybody’s been putting a lot of time and energy into this because it represents about 30% of [NSCLC]. Over the last 12 months, we’ve seen the approval of 1 drug, sotorasib, and likely a second drug later this year, called adagrasib, that will be approved for KRAS G12C lung cancer. That represents a lot of patients—a total of about 12% to 15% of all lung cancer patients. It’s a huge population, so it’s really good news for them. However, we need new KRAS inhibitors. Again, KRAS-mutated lung cancer represents about 30% of patients, but large percentage of patients still don’t have any treatments. We need a lot more treatments for them.

EBO: What are the guidelines around KRAS molecular testing and treatment selection in advanced NSCLC?

SPIRA: Now, with the approval of KRAS G12C drugs, everybody should be tested. And ideally, they’ll be tested up front, because (a) it’s nice to get all the information about all our biomarkers, and (b) a lot of clinical trials are out there for patients, as we all know. We need to find patients for all these different mutations. Everybody should be checked at the outset, but certainly before...
second-line therapy, which is where these KRAS G12C inhibitors are approved.

**EBO**: KRAS inhibitors occupy a second-line role in KRAS-positive NSCLC. When might these agents move to frontline therapy, if at all?

**SPIRA**: That’s a great question. These are currently being approved in the second-line setting, and a lot of clinical trials are now starting, and the randomized ones we believe will start later this year, in the frontline setting. There has been criticism, and rightfully so, that these targeted treatments in the second line do not work as well as the ones that we all know of, the EGFR [inhibitors] and the ALK [inhibitors], where the second-line responses are phenomenal. These are a different class of drugs: They’re GTPase inhibitors, not [tyrosine kinase inhibitors], and they just don’t work as well as the EGFR inhibitors, and that’s OK. We just need to do better. But with that in mind, there’s a lot of thought that patients might benefit more on the front line. And the real question is, which patient population? Some companies are looking at this vs chemotherapy; some are looking at it with immuno-oncology drugs. Those studies are ongoing right now, but we’re a few years away.

**EBO**: Are we potentially seeing patients fall through the cracks in situations where they have a KRAS mutation detected up front, and then it’s not necessarily being acted on after they fail first-line therapy?

**SPIRA**: Yes, not everybody has been checked. If you have somebody in the middle of the frontline therapy, if you haven’t checked, that tissue may be exhausted. That’s why it’s so important to do full NGS panels, because we’ve seen the evolution over 10 years where we have multiple drugs now that are approved that were not available before. So that’s great. Also, I think we will see more of these drugs in the frontline setting, and everybody should be checking for this right at the outset. Because, again, if you don’t know that they have a mutation, you’re not going to remember to check down the line. Probably a lot of patients in our clinic have this mutation who have never been checked, or even [if] the result is there, you just can’t find it in your [electronic medical record] because you didn’t realize the patient was tested a year-and-a-half ago.

**EBO**: How do you anticipate the treatment of KRAS mutations in NSCLC will evolve over time?

**SPIRA**: I think we’ll see a lot of efforts to get these into the frontline setting, which is very important. And I also think there will be combinations. A lot of [research is being done]—with SHP2 inhibitors, SOS1, for example. So, I think we’ll also be looking at combinations, and the first step is obviously to [study combinations] in patients who progress on a KRAS G12C inhibitor. But then secondarily looking at moving these upfront. So, can you do combinations? Because admittedly the response rates and the duration of responses are not as good. I think the other exciting thing is this [development] has really invigorated KRAS research. Forget about just KRAS G12C—we have in clinical study here 3 KRAS G12D inhibitors. A lot of new drugs are being looked at right now for different KRAS mutations, and it’s really reinvigorated this [part of the research] world.

**EBO**: What are you working on in NSCLC that you are excited to share?

**SPIRA**: No. 1 would be a lot of these new KRAS-specific studies; I think we’re seeing a lot of new targeted therapies. And No. 2, a lot of new immuno-oncology combinations. A lot of new, just phenomenal things are coming up. Angiotensin antibodies are being looked at. Some of those studies were negative, but it’s endless. We’re now looking at benign cellular therapies as well. It’s great.

**EBO**: Do you have any closing thoughts regarding KRAS-positive NSCLC to share with our audience?

**SPIRA**: Clinical trials are always number 1, always clinical trials. I think they’re great. And second, make sure you’re doing full NGS panels on your patients. You can’t put patients on a targeted therapy unless you know they have a mutation. •
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Balancing Cancer Treatment Innovation and Economic Burden

LAURA JOSZT, MA

NEW CANCER THERAPIES that improve outcomes and survival are great for patients, but they bring economic consequences, and oncologists must find a balance between providing the best care and not spending too many health care dollars, said Glenn Balasky, executive director of Rocky Mountain Cancer Centers (RMCC), as he opened the October 5, 2022, session of The American Journal of Managed Care®'s Institute for Value-Based Medicine®. The event took place in Englewood, Colorado.

Ken Cohen, MD, executive director of translational research at Optum Care, kicked off the night with a presentation on merging evidence-based medicine with data and analytics to expunge wasteful care from the system.

Cohen's chief takeaway: Not only is there no relationship between cost of care and quality of care, but “very often, they are inversely related.”

He shared a cost/quality scattergram of 1-year survival rates and total inpatient costs for Medicare beneficiaries with myocardial infarction, colon cancer, and hip fracture, which showed that when plotting cost and quality of physicians, only a few are acting at what he called the “optimal intersection of both quality and efficiency.” The goal of Optum Care's OptimalCare Model is to drive health care to that ideal intersection.

The poster child for illustrating low-value care is the thyroid cancer experience of 1999 in South Korea, in which the government decided to screen the entire population for thyroid cancer. However, the mortality for thyroid cancer was essentially zero. “Why would you design a cancer screening program for a cancer that [is associated with] no mortality? It's hard to understand that,” Cohen said.

Over a decade, there was a 13-fold increase in the diagnosis of thyroid cancer, many of which were indolent thyroid cancers that never should have been diagnosed. The result is that some patients underwent harmful care, such as thyroidectomy. “As you (can) imagine, thyroid cancer mortality didn't change at all,” he said.

The Optum Care OptimalCare Model recognizes that the solution to reducing low-value care must be led by physicians who are aligned with a physician-driven solution. It includes provider-focused, evidence-based education to help drive decisions and to bring together patients and providers for shared decision-making, so that patients understand the real-world outcomes of the care they're seeking.

Among the many examples of shared decision-making was one on breast cancer screening. Optum Care put together a document to educate women about when to start screening; at age 40 years or 50 years? The piece also included the pros and cons of starting at each age. One woman might look at the information and decide to start screening at age 40, while another will decide to wait until age 50.

"There's no right answer, as long as they make decisions based on good-quality information," Cohen said.

However, breast cancer imaging centers are marketing this decision differently. About 80% of imaging centers market mammographies to start at age 40, and few market mammographies to start at age 50. Less than 20% recommend any shared decision-making at all.

Finally, Cohen discussed the use of analytics in the OptimalCare Model. Analytical reporting is easy for a primary care provider (PCP) but is difficult at the specialty level, he explained. The PCP deals with diabetes, hypertension, hyperlipidemia, and cancer screenings, and a handful of metrics can be used to regularly follow the population being cared for. These claims-based metrics are collected to create a performance report, which is transparently shared. Individual PCPs can be compared with peers in their region over the course of time.

Can this be done for oncology? A model isn't built out yet, but Optum Care is working on one focused on patient outcomes, cost of care, and site of service. The metrics being considered include total cost of care, use of biosimilars, emergency department and hospital utilization, and optimal use of palliative care and hospice care late in the course of disease.

A Focus on Site of Care

Site of care and cost of care are things community oncology does well, said Lalan Wilfong, MD, vice president, payer relations and practice transformation, The US Oncology Network.

For the first time, cancer is the top cost driver for employers. “It's not fun being No. 1 in these settings, because when you're No. 1, you get a lot of the spotlight,” Wilfong said. “And we have to start thinking about, 'How do we manage this cost of care more effectively?'”

Right now, employers are focused on site of care management, because they want to identify the places where they can get the best value for the services provided. They're interested in second-opinion services, which tend to lower the overall total cost of care. Payers are also looking at policies related to site of service and trying to identify where they can direct patients to receive higher-value care.

Research results have shown that site-of-service cost differences emerge when comparing care in the hospital vs care in the community setting. A review of patients with breast, lung, and colorectal cancers found that, on average, care in the community cost $12,548 compared with $20,060 in the hospital setting. And 340B hospitals are even more expensive.

“So, it’s right for employers, for health plans, for [primary care provider] groups to start asking, 'Why am I paying this much more money to get the same level of care that I can get in a community-based center and a much better value?’” Wilfong pointed out.

The community practice approach to value includes numerous strategies, including the use of less expensive but equivalent medications, such as biosimilars; a focus on generics; and the use of advanced care planning and end-of-life support to drive down total cost of care, he said. Pathways, which are evidence-based and reduce variation, and state-of-the-art technology, which can deliver and attest to high-quality, cost-effective care, are also areas of focus to drive value.

Reviewing RMCC's quality performance in the Oncology Care Model, Wilfong highlighted that the practices were in the top quartile for hospice utilization before death. In addition, they had top quality scores, with inpatient visits down from 25.9% in performance period (PP) 1 to 17.9% in PP10, and emergency department (ED) visits down from 25.0% in PP1 to 21.3% in PP10.

"[There was] a marked reduction in ED visits,” Wilfong said. "Is that good enough? No, we're just getting better. And they're actively working on continuing to improve that.”
A Tool to Understand Risk
RMCC’s value-based care program also looks at whether treatment is appropriate for certain patients. The practices have implemented an assessment tool from the Cancer and Aging Research Group (CARG) to review if a patient is at high risk. If they are, the oncologist can help them understand the risks of chemotherapy before they elect to move forward with treatment.

According to Alonso Pacheco, MD, RMCC’s medical director and a medical oncologist/hematologist there, this tool provides an opportunity to have an intervention with the patient to drive a different type of behavior, and it has led to initial dose reductions that would otherwise not have occurred.

A Yale University study of the CARG tool has shown that it led to a decision to dose attenuate in 32% of cases and to a different regimen in 15% of cases. “CARG is a valuable tool” that usually takes only 5 minutes to conduct, Pacheco said. However, it requires having alternative options for patients who should choose not to receive chemotherapy after seeing their CARG score. RMCC has partnered with a local hospice company medical director to increase access to hospice care for patients, improve control of their neoplasm-related pain, and improve the transition to home hospice when the patient is ready, Pacheco added.

CARG is also now included in the National Comprehensive Cancer Network (NCCN) guidelines. In 2021, NCCN added the CARG Chemo Toxicity Calculator as a consideration to its Older Adult Oncology guidelines because of chemotherapy’s toxicity risks.

The CARG tool requests some basic information, such as age, height, and weight, as well as clinical characteristics. It also asks some functional questions, such as if the patient can walk a block, how easy it is to take their medications, and how many times they’ve fallen in the last 6 months.

When physicians near the end of life, they spend an average of 2 months on hospice; Pacheco said; however, most patients spend less than 3 days. In 2022, RMCC had 98 eligible patients with 25 on hospice; some spent more than 100 days on hospice.

“We have a tool that allows us to track the most valuable decision in medical oncology,” said Pacheco. It helps decide appropriately to not give chemotherapy to patients who will not only not benefit from it, but who might actually get sicker from it, he continued.

Currently, Anthem is reimbursing for this service, and RMCC is collaborating with other commercial payers to update contracts for reimbursement to utilize the CARG tool. However, other barriers to using the tool exist besides reimbursement. For instance, the tool is not validated for newer treatments, such as immunotherapy and oral targeted therapies.

Research confirming the tool’s value, however, is out there, Pacheco said. Yale University found that 65% of oncologists can complete the tool in 5 minutes or less, and 68% can complete it in 10 minutes or less. Ultimately, 99% of oncologists said calculating the CARG score was worth the time spent on it. In addition, a study from Kaiser Permanente Northern California found that the CARG tool predicted the risks of ED visits, hospitalizations, and mortality in patients 65 years and older.

Aligning Payers and Providers for Value-Based Cancer Care Payments

WHEN TALKING ABOUT VALUE in health care, all stakeholders must be aligned about what is being discussed and what the goals are, said Lucy Langer, MD, MSHS, national medical director, oncology and genomics, UnitedHealthcare (UHC).

“I would argue that the provider should be the arbiter of what the best care is.”

—Lucy Langer, MD, MSHS, national medical director, oncology and genomics, UnitedHealthcare

What is quality? Is it evidence-based care or outcomes-based care, or consumer-driven care? If you want to decrease cost, is that total cost of care, oncology-related spend, or some other measure? Many oncologists will see patients who receive care at multiple sites, Langer noted, and if a patient with cancer needs a hip replacement, say, should that be part of the oncology cost equation?

“Who is the arbiter of what the right metrics are?” Langer asked. The patient should always be at the center, so should the patient be the arbiter? What about the providers? “I would argue that the provider should be the arbiter of what the best care is,” Langer said, but she wondered what the role of the payer or pharma should be.

Value-based contracting in oncology falls into 2 main buckets: the Oncology Medical Home (ie, payment for doing the right thing) and episodic/bundled payments (ie, payment by condition).

At UHC, the pilot relating to episodes of care—the Cancer Episode Program—drove down costs and inpatient days compared with a national control cohort:

• Total medical costs during cancer treatment were 13% lower for patients in the program.
• Total medical costs were 22% lower for patients with metastatic cancer in the program.
• All-cause acute inpatient days during cancer care were 19% lower for patients in the program.

The pilot ran from 2015 to 2018 around a limited number of cancer diagnoses, and it was then expanded to include any authorized chemotherapy regimen. Ultimately, it included more than 40 diagnoses across 14 payment categories.

However, the challenge was that the program was too complex, and care delivery in oncology is already complex, Langer said. There is too much variability by cancer type, stage, and presentation. Then, there is too much complexity on pricing, she added, and providers were getting locked in for 2 or 3 years.

“So, we’re looking at cancer episodes and evolving it to the next thing,” Langer said, although she wouldn’t reveal what that might look like.

How do we move this along from early adopters only to broad acceptance?” Pacheco asked. “That’s our challenge.”

REFERENCES
Parsing Out the Necessary Elements for a Patient-Centric Strategy in Oncology

ALLISON INSERRO

AFTER THE TUMULTUOUS past few years, most health care leaders agree that health care equity and patient-centered care is important. How to address these issues in the face of rising costs, worse outcomes, workforce challenges, and another round of CMS pilots and regulatory changes is another matter.

“The last 2 years have really exacerbated what many of us in health care understood as problems in the delivery model,” said Ali Rahman, MBA, MHA, the practice administrator of Oncology Consultants of Houston, which partnered with The American Journal of Managed Care®’s Institute for Value-Based Medicine® for the event, held in Texas on October 11, 2022. Rahman served as moderator, and the speakers were as follows:

• Jonathan Coggins, MHA, vice president, chronic disease strategy and operations, McKesson
• Michael Kolodziej, MD, FACP, vice president and chief innovation officer at ADVI Health
• Bo Gamble, director of strategic practice initiatives at the Community Oncology Alliance (COA)
• John Sargent, MD, founding partner of BroadReach, a social enterprise health care consulting firm
• Susan Sabo-Wagner, MSN, RN, OCN, executive director of clinical strategy for Oncology Consultants
• Tesh Khullar, MBA, cofounder and president of HouseRX

Sudipto Srivastava, MS, MBA, vice president, digital solutions, Hospital for Special Surgery

During the evening, Sargent, who has spent most of his career working in impoverished countries, presented results of his organization’s first State of US Health Equity Survey.

“Recent studies by Deloitte have shown that we lose roughly $320 billion of wasted costs in the health care system every year due to social determinants of health [(SDOH)] and health inequities,” he said. Those losses will reach an estimated $1 trillion by 2040, he noted, adding that these issues also cause about $40 billion in lost productivity.1

Earlier this year, a unit of BroadReach surveyed 192 health care executives, mostly from payer organizations, to understand how organizations think about health inequities.2 The survey results indicated that while the industry sees health equity as very important, they have virtually no concrete plans to address it. Moreover, they know little about the race, ethnicity, or language of their customers or their staff, and few plan to prioritize health equity improvements in the coming year.

Organizations cited various barriers to implementing health equity initiatives, and the primary one related to data issues: lack of data, having incomplete data, and a lack of infrastructure to capture data, for starters. Other barriers included constraints due to budget, leadership, guidelines and governance, resource issues, timing and prioritization, and training and knowledge.

Sargent noted that his perspective was shaped by working in environments in which there were “extreme SDOH issues, and extreme health equity issues…[We were] trying to solve those and now we’re trying to take some of these lessons learned back into the United States.”

Organizations lack incentives to change in both the financial and regulatory realms, Sargent said.

“What can we learn from global health around health equity?” asked Rahman.

The issue with data and analytics, Sargent said, is that when you give them to a burned-out, underresourced health care manager in a country where the government spends as little as $30 or $40 per patient per year, there is no way to make sense of the information, and thus no real tools to implement anything.

“When you show a manager who’s managing multiple hospitals a bunch of cool graphs, and say, hey, you can better manage now with all these cool graphs, they just go back and they focus on what they need to do,” Sargent exclaimed. “They’ve got do too much work to interpret these graphs to see what they need to do.”

The focus needs to be on the output of the information so that each worker can be told specifically how to address current challenges, he said.

“The real issue is that people are hesitant to take action until they know what is going to happen in terms of regulations, and what is CMS going to do.”

—John Sargent, MD, founding partner, BroadReach

In addition, it is crucial to work with local groups to improve health literacy as well as to get the buy-in of trusted local leaders, in order to change health behaviors in various countries, especially those with multiple tribes and numerous official languages.

Asked what organizations can do in the United States, Sabo-Wagner replied that a patient’s zip code gives an important clue into fully understanding population health needs.

“The biggest indicator for a patient or a person—and the biggest indicator that will cause a health outcome to be bad—is their zip code. It has nothing to do with smoking or eating bad or obesity, it’s their zip code.”

Sabo-Wagner also noted that Oncology Consultants has expanded a pilot program of using community health workers with all these cool graphs, and say, hey, you can better manage now with all these cool graphs, they just go back and they focus on what they need to do.”

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“THE REAL ISSUE IS THAT PEOPLE ARE HESITANT TO TAKE ACTION UNTIL THEY KNOW WHAT IS GOING TO HAPPEN IN TERMS OF REGULATIONS, AND WHAT IS CMS GOING TO DO.”
Health equity is a required component of the latest 5-year pilots from the Innovation Center of CMS, including the Enhancing Oncology Model and the Accountable Care Organization (ACO) REACH model (Realizing Equity, Access, and Community Health). And the National Committee for Quality Assurance has created a health equity certification.

"So, it is sort of moving there. But I don't think it's moving fast enough to really compel organizations to really move," Sargent said.

"Shocking" Results on US Health Care Spending, Outcomes

Earlier in the evening, Coggins presented a familiar overview of the current woeful state of US health care spending and outcomes, as compared with other countries.

Coggins outlined McKesson's analysis of international economic data from the Organization of Economic Cooperation and Development (OECD), including health spending as a percentage of gross domestic product (GDP), health spending per capita, health care spending by category, life expectancy, health outcomes, quality of care, and the value of care.

The analysis looked at a subset of 11 of the 36 countries in the OECD with which the United States has most in common.

"The results are pretty shocking," Coggins said.

For instance, despite the fact that US health care spending is approaching almost 20% of GDP, Americans have the lowest life expectancy of residents in any Western country and the highest percentage of adults living with at least 1 chronic condition.

However, despite the bad news on every OECD metric, Coggins touted one bright spot, using a report from the Foundation for Research on Equal Opportunity (FREOPP), a free enterprise think tank that champions technological innovation.

Last year, FREOPP released an index looking at world health care innovation, which ranked countries on the metrics of fiscal sustainability, quality, and science and technology. The United States ranked first in science and technology; however, it ranked in third-from-last place in fiscal sustainability, ahead of Japan and France.

"We are anticipating that we'll shift the value-based care equation pretty substantively over the next decade, going from an exclusively value-based care plateau and shifting it to a transformative plateau," Coggins claimed. In his view, the onus will be on hospitals, because we make them a lot of money; whether it's because we're part of ACOs, which I must say to this point, have not done a very good job with oncology care; or [to] health plans or another third party. We will be held accountable," he stressed.

"Physicians are either going to be employed or subcontracted," Kolodziej said, calling it an eventual path to a single-payer health care system, if, he later clarified, nothing else improves.

"We are facing a world where I think value-based care is going to mean doing all the things we do very, very well but answering to different bosses," he said.

Kolodziej and Gamble were asked by Rahman to give their thoughts about the various payment models and their iterations. Rahman queried whether "we are going in the right direction in terms of quality and quality measures. What does that actually means in terms of quality for the patient? Are all these models moving in that direction?"

To no one's surprise, both panelists were critical.

"They're incredibly complex," Gamble said of the models. "I would like to see someone that's got a great model that's some-what simple, that people could say, yes, I can follow that, and I can implement that. But so far, nothing is transferable, is scalable, for other people to do it," he said.

Quality measures, Kolodziej added, are mostly an afterthought.

"And part of that, honestly, it's our fault—our fault being us, the oncologists, because we actually have been unable to articulate what quality means in a cancer patient."

Patient Access to Data

Rahman ended the evening with a discussion seeking some practical takeaways with Khullar and Srivastava, after their respective presentations about future trends, including pharmacy benefit managers and the push for transparency, the Inflation Reduction Act (IRA), and improvements to watch for in digital health.

Implementing the IRA will take 3 election cycles, Khullar said, but another notable event to watch for is the part of the 21st Century Cures Act that took effect on October 6, which ends so-called information blocking of health data. The Cures Act directs the Office of the National Coordinator for Health Information Technology to create a standardized process through which patients can request access to all of their electronically protected health information in designated record sets.

Start-up companies likely will create opportunities to help consumers pull their information from different sources and make sense of it, said Srivastava, who also said he is looking forward to the transparency enabled by the Cures Act.

REFERENCES


**INDICATION AND USAGE**

**Indication:** 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.

**Limitations of Use:** NINLARO is not recommended for use in the maintenance setting or in newly diagnosed multiple myeloma in combination with lenalidomide and dexamethasone outside of controlled clinical trials.

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**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

- **Thrombocytopenia** has been reported with NINLARO. Platelet nadirs typically occurred between Days 14-21 of each 28-day cycle and recovered to baseline by the start of the next cycle. Grade 3 thrombocytopenia was reported in 17% of patients in the NINLARO regimen and Grade 4 thrombocytopenia was reported in 13% in the NINLARO regimen. 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.

- **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.

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Please see additional Important Safety Information on the next page and accompanying Brief Summary.

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**IMPORTANT SAFETY INFORMATION (cont’d)**

**WARNINGS AND PRECAUTIONS (cont’d)**

Diarrhea resulted in the discontinuation of one or more of the three drugs in 3% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms.

- **Peripheral Neuropathy** was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (24% and 17% 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 4% of patients in the NINLARO regimen and <1% of patients in the placebo regimen. During treatment, monitor patients for symptoms of neuropathy and consider adjusting dosing for new or worsening peripheral neuropathy.

- **Peripheral Edema** was reported with NINLARO. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of NINLARO for Grade 3 or 4 symptoms or dexamethasone per its prescribing information.

- **Cutaneous Reactions**, including a fatal case of Stevens-Johnson syndrome, were reported with NINLARO. If Stevens-Johnson syndrome occurs, discontinue NINLARO and manage as clinically indicated. 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 if Grade 2 or higher.

- **Thrombotic Microangiopathy** has been reported with NINLARO. Fatal cases 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 reintimating NINLARO therapy in patients previously experiencing TTP/HUS is not known.

- **Hepatotoxicity** has been reported with NINLARO. Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in <1% of patients treated with NINLARO. Hepatotoxicity has been reported (10% in the NINLARO regimen and 9% in the placebo regimen). Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms.

- **Embryo-fetal Toxicity**: NINLARO can cause fetal harm. 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 last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the last dose.

- **Increased Mortality in Patients Treated with NINLARO in the Maintenance Setting**: In two prospective randomized clinical trials in multiple myeloma in the maintenance setting, treatment with NINLARO resulted in increased deaths. Treatment of patients with NINLARO for multiple myeloma in the maintenance setting is not recommended outside of controlled trials.

**ADVERSE REACTIONS**

The most common adverse reactions (≥ 20%) in the NINLARO regimen compared to placebo in combination with lenalidomide plus dexamethasone, respectively were thrombocytopenia (85%, 67%; pooled from adverse event and laboratory data), neutropenia (74%, 70%; pooled from adverse event and laboratory data), diarrhea (52%, 43%), constipation (35%, 28%), peripheral neuropathy (32%, 24%), nausea (32%, 23%), edema peripheral (27%, 21%), rash (27%, 16%), vomiting (26%, 13%), and bronchitis (22%, 17%). Serious adverse reactions reported in ≥ 2% of patients in the NINLARO regimen included diarrhea (3%), thrombocytopenia (2%), and bronchitis (2%).

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

**USE IN SPECIFIC POPULATIONS**

- **Lactation**: Advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.

- **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.

Please see additional Important Safety Information on the previous page and accompanying Brief Summary.

1 INDICATIONS AND USAGE
NINLARO (ixazomib) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Limitations of Use: NINLARO is not recommended for use in the maintenance setting of newly diagnosed multiple myeloma in combination with lenalidomide and dexamethasone outside of controlled clinical trials.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Thrombocytopenia: Thrombocytopenia has been reported with NINLARO with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. Grade 3 thrombocytopenia was reported in 17% of patients in the NINLARO regimen and Grade 4 in 13% of the NINLARO regimen. The rate of platelet transfusions was 10% in the NINLARO regimen and 7% in the placebo regimen. Monitor platelet counts at least monthly during treatment with NINLARO. Consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.

5.2 Gastrointestinal Toxicities: Diarrhea, constipation, nausea, and vomiting have been reported with NINLARO, occasionally requiring use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea was reported in 52% of patients in the NINLARO regimen and 43% in the placebo regimen, constipation in 35% and 28%, respectively, nausea in 32% and 23%, respectively, and vomiting in 26% and 13%, respectively. Diarrhea resulted in discontinuation of one or more of the three drugs in 3% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms.

5.3 Peripheral Neuropathy: The majority of peripheral neuropathy adverse reactions were Grade 1 (18% in the NINLARO regimen and 16% in the placebo regimen) and Grade 2 (11% in the NINLARO regimen and 6% in the placebo regimen). Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens. The most commonly reported reaction was peripheral sensory neuropathy (24% and 17% 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 4% of patients in the NINLARO regimen and <1% of patients in the placebo regimen. Patients should be monitored for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy may require dose modification.

5.4 Peripheral Edema: Peripheral edema was reported in 27% and 21% of patients in the NINLARO and placebo regimens, respectively. The majority of peripheral edema adverse reactions were Grade 1 (17% in the NINLARO regimen and 14% in the placebo regimen) and Grade 2 (7% in the NINLARO regimen and 6% in the placebo regimen). Grade 3 peripheral edema was reported in 2% and 1% of patients in the NINLARO and placebo regimens, respectively. Peripheral edema resulted in discontinuation of one or more of the three drugs in <1% of patients in both regimens. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.

5.5 Cutaneous Reactions: Rash was reported in 27% of patients in the NINLARO regimen and 16% of patients in the placebo regimen. The majority of the rash adverse reactions were Grade 1 (15% in the NINLARO regimen and 9% in the placebo regimen) or Grade 2 (9% in the NINLARO regimen and 4% in the placebo regimen). Grade 3 rash was reported in 3% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Serious adverse reactions of rash were reported in <1% of patients in the NINLARO regimen. The most common type of rash reported in both regimens included maculo-papular and maculopapular rash. 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 if Grade 2 or higher. Stevens-Johnson syndrome, including a fatal case, has been reported with NINLARO. If Stevens-Johnson syndrome occurs, discontinue NINLARO and manage as clinically indicated.

5.6 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 restarting NINLARO therapy in patients previously experiencing TTP/HUS is not known.

5.7 Hepatotoxicity: Drug-induced liver injury, hepatoceleular injury, hepatic steatosis, hepatocellular and hepatocholastic and hepatotoxicity have each been reported in <1% of patients treated with NINLARO. Hepatotoxicity has been reported (10% in the NINLARO regimen and 9% in the placebo regimen). Monitor hepatic enzymes regularly and 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 of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the last dose.

5.9 Increased Mortality in Patients Treated with NINLARO in the Maintenance Setting: In two prospective randomized clinical trials in multiple myeloma in the maintenance setting, treatment with NINLARO resulted in increased deaths. Treatment of patients with NINLARO for multiple myeloma in the maintenance setting is not recommended outside of controlled trials.

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 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=361) or placebo in combination with lenalidomide and dexamethasone (placebo regimen; N=359).

The most frequently reported adverse reactions (≥20% with a difference of ≥5% compared to placebo) in the NINLARO regimen were thrombocytopenia, neutropenia, diarrhea, constipation, peripheral neuropathy, nausea, peripheral edema, rash, vomiting, and bronchitis. Serious adverse reactions reported in <2% of patients in the NINLARO regimen included diarrhea (3%), thrombocytopenia (2%) and bronchitis (2%). One or more of the three drugs was permanently discontinued in 4% of patients reporting peripheral neuropathy, 3% of patients reporting diarrhea, 2% of patients reporting thrombocytopenia. Permanent discontinuation of NINLARO due to an adverse reaction occurred in 10% of patients.

Table 4 summarizes the non-hematologic adverse reactions occurring in at least 5% of patients with at least 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>System Organ Class / Preferred Term</th>
<th>NINLARO + Lenalidomide and Dexamethasone N=361 (%)</th>
<th>Placebo + Lenalidomide and Dexamethasone N=359 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>All Grades</strong></td>
<td><strong>Grade 3</strong></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>52</td>
<td>10</td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy†</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Maculopapular and connective tissue disorders</td>
<td>27</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Back pain*</td>
<td>27</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection*</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>Urticaria†</td>
<td>27</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: Adverse reactions included as preferred terms are based on MedDRA version 21.0.

*At the time of the final analysis, these adverse reactions no longer met the criteria for a ≥5% difference between the NINLARO regimen and the placebo regimen.

†Represents a pooling of preferred terms

(Continued on next page)
Brief Summary (cont’d)

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

<table>
<thead>
<tr>
<th>NINLARO + Lenalidomide and Dexamethasone</th>
<th>Placebo + Lenalidomide and Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=361</td>
<td>N=359</td>
</tr>
<tr>
<td>Any Grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>85</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>74</td>
</tr>
</tbody>
</table>

5.1 Thrombocytopenia: 
Thrombocytopenia has been reported with NINLARO in 17% of patients treated with NINLARO: acute febrile neutrophilic dermatosis (Sweet’s syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura.

6.1 Clinical Trials Experience: 
Common adverse reactions were Grade 1 (18% in the NINLARO regimen and 16% in the placebo regimen). Grade 3 adverse reactions were reported at a frequency of <1% in patients treated with NINLARO: acute febrile neutrophilic dermatosis (Sweet’s syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura.

5.2 Lactation: 
There are no data on the presence of ixazomib or its metabolites in human milk, the effects of the drug on the breast fed 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.

5.3 Peripheral Neuropathy: 
Peripheral neuropathy was reported in 27% and 21% of patients in the NINLARO and placebo regimens, respectively. The majority of peripheral neuropathy reactions were Grade 1 (17% in the NINLARO regimen and 16% in the placebo regimen). Grade 3 adverse reactions of peripheral neuropathy were reported at a frequency of <1% in patients treated with NINLARO: acute febrile neutrophilic dermatosis (Sweet’s syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura.

5.4 Renal Impairment: 
In patients with severe renal impairment or ESRD requiring dialysis, the mean AUC increased by 25% when compared to patients with normal renal function. Reduce the starting dose of NINLARO in patients with moderate or severe renal impairment.

5.5 Cutaneous Reactions: 
Cutaneous reactions were Grade 1 (17% in the NINLARO regimen and 16% in the placebo regimen). Grade 3 cutaneous reactions were reported at a frequency of <1% in patients treated with NINLARO: acute febrile neutrophilic dermatosis (Sweet’s syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, herpes zoster, cataract, dry eyes, blurred vision, conjunctivitis and thrombotic thrombocytopenic purpura.

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

8.2 Lactation: 
There are no data on the presence of ixazomib or its metabolites in human milk, the effects of the drug on the breast fed 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.

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

7.2 Strong CYP3A Inhibitors: 
Avoid concomitant administration of NINLARO with strong CYP3A inhibitors (such as ritonavir, saquinavir, and clarithromycin) and moderate CYP3A inhibitors (such as erythromycin, and fluconazole).

7.3 Other Interactions: 
NINLARO should not be used concomitantly with other drugs that are likely to cause neurologic effects.

9.2 Adverse Reactions: 
Adverse reactions were reported at a frequency of <1% in patients treated with NINLARO: acute febrile neutrophilic dermatosis (Sweet’s syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, herpes zoster, cataract, dry eyes, blurred vision, conjunctivitis and thrombotic thrombocytopenic purpura.

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). 

Dosage Instructions: 
- Instruct patients to take NINLARO exactly as prescribed.
- Advise patients to take NINLARO once a week on the same day and 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 [see Overdosage (10)].
- 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. [see Dosage and Administration (2.1)].

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 any signs 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 (5.5)].

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

Liver Toxicity: 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 any signs or symptoms of acute febrile neutrophilic dermatosis (Sweet’s syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, herpes zoster, cataract, dry eyes, blurred vision, conjunctivitis 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 last 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 last dose [see Use in Specific Populations (8.1)].

Lactation: Advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose (see Use in Specific Populations (8.1)).

Concomitant Medications: Advise patients to speak with their healthcare providers about any other medication they are currently taking and before starting any new medications.
Astera Cancer Care Shows How Community Oncology Can Innovate Both in the Clinic and in Contracting

MARY CAFFREY

CONTINUED FROM SP524

IVBM EDISON

AS NEW CANCER THERAPIES or indications seem to arrive every week, the world of community oncology has felt the ground shift. Community oncology still delivers 80% of cancer care, but keeping pace with innovation means no one can stand still, said Edward J. Licitra, MD, PhD, CEO of Astera Cancer Care, as he opened the November 3, 2022, session of the Institute for Value-Based Medicine® in partnership with *The American Journal of Managed Care*.

"Many people look at a cancer care or an oncology practice, and they see a practice," Licitra said. "We really have rethought that. We are a practice, but we like to see ourselves as a platform.

By platform, Licitra means building an infrastructure to offer patients the same cutting-edge care as an academic center, but with greater convenience—and for payers, at a lower cost. In early 2021, Licitra and Bruno Fang, MD, Astera’s president and director of clinical research, along with 35 other medical and radiation oncologists in Central New Jersey, left another multistate practice to form Astera and aligned with OneOncology, a network of 15 practices based in Nashville, Tennessee, that offers technology support, clinical pathways, and a clinical trial consortium.

"Once we have the platform, which we have now, we want to use the platform to do innovative clinical care," Licitra said. "And the next thing that you have to do is innovate when it comes to contracting."

The 2 go “hand in hand,” he said, because as clinical innovation continues, there is an ongoing need to optimize how to pay for care. That means working with payers on unique structures that keep a practice viable while limiting the resources spent on time-consuming tasks, such as prior authorization.

As Licitra and other speakers later discussed, Astera and Horizon Blue Cross Blue Shield of New Jersey have pursued groundbreaking episode of care payment models that may now extend to treatments such as chimeric antigen receptor (CAR) T-cell therapy. These are programs, Licitra said, “that I don’t think anybody else in the country has developed.” (See *SP525*).

Clinical Trials in the Community

The IVBM event took place in Edison, New Jersey, a town named for the state’s most famous inventor, one who set in motion the region’s tradition of basic science that is now seen in the presence of global pharmaceutical giants and emerging biotechs. Proximity yields partnerships: Astera, based nearby in East Brunswick, was the lone community oncology practice to take part in a clinical trial for Bristol Myers Squibb’s CAR T-cell therapy, isocabtagene maraleucel; Licitra was a coauthor on a recent article in *The Lancet Oncology*. Astera’s practice locations are not far from academic centers, whose relationship with community oncology has shifted, as Fang explained.

The changing landscape in science, in business models, and in patient needs demands that patients have an option to take part in clinical trials at the community practice level, he said.

Just a day earlier, Fang said he had been at a dinner where a director of a National Cancer Institute–designated Cancer Center suggested that if Astera had patients eligible for phase 1 trial, “you can send the patients to us.”

Fang replied, “We have phase 1 trials.”

Twenty years ago, drug development was dominated by academic centers; Fang said it was all but impossible for a community oncologist to break into a collaborative research group. Over time, as partnerships with industry increased, there was more effort to “democratize” trials, which required collaboration with community oncologists for patient referrals. In return, he said, academic centers sent patients who needed standard of care back to the community.

But more recently, collaboration has soured, as academic centers have bought up practices, employing oncologists to treat the standard of care patients. “The academic centers, which used to be our partners, have become our competitors,” Fang said.

Meanwhile, the number and diversity of trials have exploded, and Fang and Licitra see the added layers of bureaucracy in academic centers as adding time and cost to a process that community practices can run more efficiently. Pharmaceutical companies should weigh these factors as they seek research partners, Fang said. Community practices such as Astera have responded by increasing in scale and adding the personnel to handle research; Fang noted that Astera is part of OneOncology’s OneR network and has 45 trials running currently.

For payers, working with community oncology practices that offer clinical trials maximizes benefits: Patients receive access to cutting-edge science and therapies and diagnostics at reduced cost, and close monitoring of toxicities.

"Why should you work with us?" he asked. The main advantage, he said, is time: An academic center may take a year to start a trial that Astera can launch in 2 months. Companies investing “billions of dollars” should not have to wait more than a year to start a trial.

Community practices can also promote diversity in trials, he said. Just navigating the parking lot at a large academic center is time-consuming and a deterrent for some patients. So trials at academic centers tend to get patients who are younger, healthier, and not representative of the population, Fang said.

For payers, Fang said, working with community oncology practices that offer clinical trials maximizes benefits: Patients receive access to cutting-edge science and therapies and diagnostics at reduced cost, and close monitoring of toxicities. A study by Tennessee Oncology, another OneOncology practice, found that when patients in an Oncology Care Model (OCM) were taking part in a clinical trial, the cost based on 6-month episodes of care was 18% lower than the average cost of a 6-month episode outside of a trial.
Approaches to Maintenance After MM Treatment

The abundance new therapies and combinations has significantly increased the average life span for patients newly diagnosed with multiple myeloma (MM) over the past 20 years, but it has also raised an important question: Is it ever safe to stop maintenance therapy?

M. Hossein Kazemi, MD, a medical oncologist and hematologist at Astera, addressed this question in a discussion on the use of minimal residual disease (MRD) testing, which can find whether cancer cells remain in the bone marrow after treatment. The testing can both confirm remission and detect an early return of cancer, and Kazemi discussed an important trial studying how novel therapeutic regimens combined with MRD testing could lead to new protocols. This could free certain MM patients from indefinite maintenance therapy, with important implications for payers and for quality of life.

The phase 2 MASTER trial (NCT03224507), reported in 2021, combined daratumumab, carfilzomib, lenalidomide, and dexamethasone in patients with newly diagnosed multiple myeloma, then used MRD testing by next-generation sequencing to decide the use and duration of the therapeutic combination post-autologous hematopoietic cell transplantation (AHCT).

"Instead of the conventional myeloma treatment paradigm—induction, transplant, maintenance until progression—they gave intensive treatment upfront. They gave 4 cycles at induction, then they checked the marker," Kazemi explained. Patients then went to AHCT; then minimal residual disease was checked. Those with 2 consecutive negative residual disease tests went to observation; others had another 4 cycles. If residual disease negativity was not achieved, these patients went to lenalidomide maintenance.

So far, 2-year progression-free survival rates are 91% or higher for those who achieved minimal residual disease negative results early.

While more data are needed, Kazemi said, "we might be approaching a new paradigm" for management after initial treatment. It appears if minimal residual disease negativity is achieved early, a patient will "probably do very well long term."

So, do these patients need maintenance therapy to avoid progression? "That's the subject of several ongoing trials," he said. By contrast, the patients who do not achieve MRD negative status may need more intensive therapy.

Managing Risk in the Era of Value-Based Care

Astera's foray into value-based care programs meant moving away from a traditional fee-for-service environment, and that meant taking on risk. Whether the practice pursues episodes of care or Medicare's Oncology Care Model (OCM), transitioning to upside only (1-side) and then to 2-sided risk demanded a change of mindset and financial modeling beyond most practices' traditional scope of responsibility. For Astera and like-minded practices, the idea of improving patient care was not the issue. However, assuming risk was new territory.

"It really comes down to who's going to ultimately take the risk for the health of the patients. That's what value-based care is all about," said presenter Brian S. Kern, JD, who is of counsel for the law firm Frier Levitt and a veteran of the medical malpractice and professional liability insurance sectors.

In 2018, Kern saw that CMS' commitment to value-based models meant physicians needed help evaluating risk and finding properly priced stop-loss insurance and founded Deep Risk Management. Both OCM and the proposed Enhancing Oncology Model (EOM) have created a need for oncologists to find risk-sharing solutions if they want to participate in the next phase of practice transformation.

As Kern noted, the finances of the EOM appear more daunting than those of the OCM, which paid $160 per patient per month to deliver enhanced services. The EOM, set to start July 1, 2023, will pay $70 per patient per month for those services, with an extra $30 if the patient is Medicaid-eligible. But that's not the most important part, Kern explained. "The big thing is, even though it's not a tremendous amount of risk, you have to take risk right off the bat at 2%," with an upside possibility of 6%. The EOM offers a second tier of higher risk, higher reward.

Pursuing a value-based care relationship without a good payer relationship is difficult, Kern said, because it works requires data sharing and cooperation with a partner who understands the data structure. But taking on risk can be worth it. "I really believe the more risk we take, the more control you have over the continuum of care," he said.

While the concepts Kern was presenting—using insurance to smooth out the good years and the bad years—are not new, they are still relatively recent in oncology, and for that reason gathering good data and using good analytics will be extremely important. But Kern was very clear about what his firm would and would not do.

"We believe value-based care is all about the ability to control risk; that's how we approach this industry." But once the results of data analytics are available, he said, "I'm not going to call in and say 'Hey, you should change your practice patterns based on some of my research.' "

Once the data are available, it will be up to physician leaders to recommend changes at the practice level. Data will help physicians stratify patients based on risk levels, to prevent incidents most likely to result in hospitalization or added expense. "We do believe that variation can be controlled," Kern said.

INNOVATIONS IN CONTRACTING

Breaking New Ground in Episodes of Care, Including CAR T-Cell Therapy

Mary Caffrey

PROSPECTIVE PAYMENTS in episodes of cancer care? Bundled payments in chimeric antigen receptor (CAR) T-cell therapy, at a fraction of the current cost?

Yes, it's possible, said Edward J. Licitra, MD, PhD, CEO of Astera Cancer Care, the East Brunswick, New Jersey-based multisite practice that joined OneOncology in early 2021. During a session of the Institute of Value-Based Medicine® presented on November 3, 2022, with The American Journal of Managed Care®, Licitra highlighted groundbreaking oncology payment models with Horizon Blue Cross Blue Shield of New Jersey that promise to deliver on all of the elements of the quadruple aim: better care, reduced costs, improved patient experience, and greater satisfaction for physicians.

Licitra led a discussion with Joseph M. Pepek, MD, a radiation oncologist with Astera, and Joe O’Hara, MBA, a business consultant who until October was director for Horizon Healthcare Innovations, an arm of the payer that develops innovative payment models. The 3 addressed a model for early stage breast cancer developed by Astera in collaboration with Horizon that covers the episode from initial diagnosis through intermediate care, including any surgical and post-surgical care, lab work, and radiology.

As Licitra explained, a single prospective price is paid for the entire episode, whether it lasts 6 months, 9 months, or 12 months. Astera continued
CONTINUED FROM PREVIOUS PAGE

provides treatments, radiation, surgery, follow-up, and home care. The model draws on Astera’s experience with the Oncology Care Model but is distinctly different, as that model offers shared savings months after the episode ends.

Receiving payment upfront puts the onus on the practice to appropriately manage the patient. “You essentially go at-risk,” Licitra said. “It’s kind of a form of mini-capitation,” based on a distinct population.

Why would a payer agree to this? O’Hara explained that the biggest advantage comes from locking in costs. From an actuarial standpoint, he said, both payer and practice can anticipate how many patients the practice will have with a given diagnosis over a given period, and estimate what the costs will be. Under most shared savings models, if you’re the payer, “you’re not necessarily locking in your costs, and you’re still carrying those outlier patients.”

The shift to prospective payments gives providers incentives to take actions that will drive down costs over time, O’Hara said. If successful: “The provider captures all the savings, and the payer gets the benefit of essentially eliminating those patients from a cost standpoint.” Reinsurance can be used to handle outliers (See SP524).

When Astera approached Horizon with this concept, both sides had significant experience with value-based care, and Horizon had experience in episodes of care in 160 different clinical areas. The trend, O’Hara said, is that “the providers who are working in the episodes have significantly better outcomes than the providers who are not.”

It’s not fully understood why practices that participate in episodes of care programs report better outcomes, he said, but the data show that engaging in the models makes a difference. “Almost universally, the episode partners do better.”

Pepek said it made sense to him that this multidisciplinary breast cancer model would work in community oncology. The practice design is less fragmented than an academic center, and he said the communication is stronger.

He credited the relationships built with the Horizon team, and the common goal of keeping the patient at the center, “but at the same time helping to reduce some of the financial burden and the administrative burden—for both the patient and the practice.” It helps that Astera has a freestanding radiation center, with lower costs than might be seen in a hospital, he said.

Pioneering Models in CAR T-Cell Therapy

Licitra finished the program with an overview of CAR T-cell therapy and Astera’s participation in a clinical trial involving Bristol Myers Squibb’s lisocabtagene maraleucel (liso-cel), sold as Breyanzi. The first CAR T-cell therapy was approved in 2017, and these treatments have since proved to be lifesaving for patients who have run out of options for certain lymphomas and leukemias, and more recently, for multiple myeloma. But the wonders of CAR T-cell therapies were offset by their practical and financial realities. The toxicity once made hospitalization a must, and the costs, which started at $373,000 just for the treatment, could run as high as $1.5 million per patient with hospitalization, Licitra said.

Over time, oncologists have learned more about managing those toxicities. And scientists have described liso-cel’s manufacturing process as one that results in a product with less toxicity than its predecessors for treating lymphoma.

“Since the side effect profile is much better, we can begin to think about different ways to administer CAR T cells,” Licitra said. “As we have more and more control over which CAR T cells we can use—which ones have a better side effect profile—and as we become more well-versed in terms of how to down-regulate the toxicity, should it arise, you can begin to see that maybe everybody doesn’t need to go to the hospital anymore.”

This shift is important and much anticipated, because in the past year CAR T-cell therapy has been approved in earlier lines of care. To broaden the reach of who can access CAR T-cell therapy, many believe that community oncology must administer treatments for fitter eligible patients.

“Now, if you make it even more interesting, CAR T cells are just the first of many cellular therapies that are going to be developed. So that’s why we talk about cellular therapies,” Licitra said. “There are 300 cellular therapies that are in development. Some are autologous CAR T cells; some are allogeneic CAR T cells, which are CAR T cells off the shelf; but there are NK [natural killer] cells; and there are tumor-infiltrating lymphocytes; and there are bispecific T-cell engaging antibodies. And then there’s CRISPR, gene-editing directed therapy…. But all these amazing therapies are going to come with a very, very steep price tag.”

As Licitra thought through this problem, he said: “We’ve got to develop a different way of giving CAR T cells or expensive cellular therapies, so that every patient that needs one has the ability to get one—because what would be the worst thing that could happen is that we’ve got great therapies that cure people of cancer that are being moved into earlier lines of therapy, but patients can’t get access to them. Where they’re just so expensive, nobody wants to pay for them.”

Once Astera had taken part in the clinical trial with liso-cel, Licitra said the next question for Astera was: How do we take the next step? “How do we actually innovate from the perspective of reimbursement?”

“As you’ve heard, we’re all about episodes of care,” he continued. The next logical step would be to develop an episode of care model that could dramatically reduce the cost of CAR T-cell therapy administration and, in the process, prove to be a game changer with New Jersey’s largest payer, which has 3.8 million members.

Licitra said Astera was very close to completing a 6-month care episode with Horizon that he estimated would reduce costs by as much as 40%, depending on the pricing of CAR T-cell therapies in the market.

“So, from the time a patient was identified as being a candidate for CAR T-cell therapy, could we do everything that patient needed within a 6-month window?” Licitra asked. This would include determining a patient’s eligibility for CAR T cell therapy, contracting for apheresis, collecting the patient’s T cells, and sending them to the manufacturer for the engineering process, which takes 6 to 8 weeks.

“These are patients with advancing cancers, so we have to give them lymphocyte-depleting chemotherapy; infuse the CAR T cells in our office; monitor them for toxicity and, if they needed to be admitted to a hospital, make sure we have all that infrastructure in place with our partner hospital; then do all the scans for 3 months following the CAR T-cell [administration] to see if they have responded.”

Licitra said: “We have all the capabilities to do it. We have all the relationships to do it. Now it becomes, how do we do it? And how do we price it?”

There is great excitement about this possibility, he said, from partners that work with self-insured employers; they envision flying patients in from out of state and housing them in a nearby long-term stay hotel.

“This is all about collaboration and relationships and people coming together to create value disruptions in health care,” Licitra said. “Health care has really been dominated by people that have had tunnel vision. Nobody wants to work with anybody else, and will never be able to solve the big problems unless we’re all working together.”

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CONTINUED FROM SP525

Data can also be used to determine whether certain therapies are costing practices money, to measure the impact of certain billing codes for patient comorbidities, and to see whether some situations are best managed with in-home care. Deep Risk Management built dashboards to make it easier to present these data to clients. “We wanted this to be a collaborative process,” he said. “So we had to build out a lot of capabilities that didn’t otherwise exist.”

Kern is clear on the role of risk management in value-based care. “We’re not interested in being a data analytics company. We’re not interested in being a care coordinator,” he said. “But we’re very interested in understanding all the levers at play, to make sure these programs are successful.”

Assessing Social Determinants of Health

Achieving equity in cancer care outcomes starts with assessing social determinants of health (SDOH), said Ellen A. Ronnen, MD, who is Astera’s chief medical officer. As the American Society of Clinical Oncology (ASCO) and other groups address health equity on a global scale, Ronnen said much can be done at a practice level.

“I have patients who reach out to me and ask, ‘do you have an interpreter? Do you have translation services?’ And I say, well yes and no,” she said. “Well, yes, we do have them, but we’re not using them, and we’re not designed around them. And so, it’s much more valuable for the patient, she said. Translating services, meanwhile, provide the ability to translate documents into the language of a patient’s choice, from informed consent to education materials, to information on office locations.

Interpreter and translation services offer a vivid example of how overcoming language barriers—-or failing to do so—can make a difference in a patient’s ability to access care. When patients lack interpreters, Ronnen said, research shows they fail to access care due to feelings of inadequacy about their ability to engage with the health care system.

The NCCN Distress Thermometer “can identify potential obstacles,” whether they are financial, or insurance barriers, or transportation issues, Ronnen said, allowing the practice to connect patients to a service or provide a referral to an outside agency. She shared data presented at the 2022 ASCO Quality Care Symposium, in which assessments were used to identify patients who reached a "trigger score" for referral to the social work department. Individual psychotherapy and group therapy, in addition to being beneficial to patients, are billable services, Ronnen said.

“There was uncredible uptake. Patients are very interested in using these services,” she said. But addressing SDOH also comes down to asking the right questions. Arranging transportation might go beyond setting up a ride, to making sure a patient can get down a flight of stairs, for example. A patient advisory board can identify barriers to poor trial enrollment and gaps in quality of care.

“And I would say educate, educate, educate staff on equity-related content, because we all have so much to learn,” Ronnen said.

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From Cancer Prevention to Treatment: Underpinning the Advances, Challenges to Democratizing Precision Oncology

MATTHEW GAVIDIA

IVBM VANDERBILT

PRECISION ONCOLOGY HAS LONG influenced the management of common and rare cancers, in which stage of disease and pathology have been used to inform treatment strategies that aim to align with respective care needs. However, only recently have advances in precision medicine and screening expanded the possibilities of treatment for patients beyond the one-size-fits-all approach of chemotherapy and into a personalized care plan where the vulnerabilities of each particular cancer are prioritized and targeted.

BRAF, EGFR, and KRAS G12C mutations, identified via genomic testing, are some of the known targets that have led to therapeutic breakthroughs for solid and hematologic malignancies. And there is hope that precision medicine can be democratized to every single patient with cancer, said Doug Johnson, MD, MSCI, associate professor of medicine and director of precision oncology at Vanderbilt-Ingram Cancer Center, but several challenges remain that continue to limit its effectiveness in oncology.

Johnson and Ben Ho Park, MD, PhD, professor of medicine and director of Vanderbilt-Ingram Cancer Center, served as cochairs of The American Journal of Managed Care® Institute for Value-Based Medicine® event in Nashville, Tennessee, held November 17, 2022. The event was held in partnership with Vanderbilt-Ingram Cancer Center. The event addressed several topics in precision oncology, including novel treatment options, microsatellite instability (MSI) in gastrointestinal (GI) cancers, and precision treatments for smoking cessation. Examples of precision medicine success and best practices in leveraging structured genomic data were also discussed.
Novel Treatment Options and Challenges in Precision Oncology

The introduction of genetic and genomic testing tools, such as next-generation sequencing (NGS), has helped to provide a more personalized and precise approach to treatment for patients with cancer, noted Johnson. However, as shown in the NCI-MATCH trial, not all patients who undergo sequencing show a mutation that can be targeted with immunotherapy.1

"Many patients didn't have a [mutation] that could be targeted—somewhere in the range of 75%. The response rates on some arms were very low, and many patients that responded had short lived responses. With that being said, there were certainly some great successes, but I think it sort of demoralized some people who were hoping for big wins," he said.

Nonetheless, steady progress continues to be made in the precision oncology field. Targets that were previously thought to be undruggable, such as KRAS G12C mutations, have seen therapeutic success with drugs like sotorasib.

More targets, better drugs, and better options for resistance have expanded precision oncology beyond the "1 gene, 1 drug" paradigm, noted Johnson, and clinical research efforts seek to improve the generalizability of specific success stories to entire populations of patients with these diseases.

Management of non–small cell lung cancer (NSCLC) is a field that has seen notably significant progress in the recognition of mutations involved with development and progression, as well as novel targeted drugs and immunotherapies associated with improved patient outcomes.

The DESTINY-Lung01 trial findings demonstrated the efficacy of trastuzumab deruxtecan (T-DXd) in patients with HER2-mutant advanced NSCLC, providing improved response rates, progression-free survival (PFS), and overall survival (OS).2

The development of newer, more rationally designed targeted therapies also translates to other tumors that express the same mutations, said Johnson. For example, significant improvement in PFS and OS is also shown with T-DXd in HER2-low metastatic breast cancer.2

“One thing that’s exciting is that as we continue to identify these targets, we’re moving even beyond tumor DNA," Johnson said. “Of course, that’s a powerful tool to do the sequencing and identify these mutations, but we really need even better options.”

A major challenge facing cancer centers who are shifting their care pathways toward precision medicine is deciding which kind of tests to order, Johnson explained.

Various types of genetic abnormalities beyond driver mutations exist in solid and hematologic tumors, including chromosomal abnormalities, mutational processes, and tumor heterogeneity, and the ability to detect these abnormalities depends on the test design and validation process utilized.3

At Vanderbilt-Ingram Cancer Center, Johnson said tests are selected on a case-by-case basis, and the choice depends on factors such as the amount of tumor tissue available. Another challenge is interpreting the results of these tests.

“One thing that we’ve done is that we’ve established molecular tumor boards, including an internal one where we have a panel of people who think about this a lot, and also disease specific experts and hereditary cancer experts who all can review a case, review genetic results, and then provide a recommendation."4

Ultimately, leveraging these data can lead to the selection of appropriate treatments and the advancement of precision oncology. But Johnson said that clinicians should expand their goals to also strive for precision health, which assesses immune function and status, the microbiome, and vital signs, among other clinical features.

Studies are just beginning to scratch the surface in determining the impact of the microbiome on the efficacy of certain immunotherapies and overall human health, said Johnson.

“The goal is not just to treat cancer, but to give people long, healthy, happy, flourishing lives," he noted. “The lessons we can learn with [precision oncology] can hopefully lead to that.”

Implications of MSI on Prognosis, Therapy in GI Cancers

Focusing primarily on colorectal cancer (CRC) and the MSI mutation, Kristen K. Ciombor, MD, MSCI, an associate professor of medicine at Vanderbilt-Ingram Cancer Center, next addressed emerging data in the localized setting.

Recent advances in screening through NGS and other technologies have identified a myriad of actionable mutations in colorectal cancer. The MSI subtype, also known as mismatch repair deficiency, affects a relatively small number of patients with colorectal cancer, but it is an important biomarker across all tumor types, said Ciombor.

“We know that mutations encode proteins that can be recognized and targeted by the immune system, and average tumors actually only have a few somatic mutations, but MSI-high tumors have thousands of mutations and we actually can use that to our advantage," she explained.

“The hypothesis many years ago was that the immune micro-environment was counterbalanced by these inhibitory signals that resisted tumor elimination. And if you could augment with programmed cell death protein 1 (PD-1) blockade, you could potentially have more success with treatment, especially with these MSI tumors,” Ciombor pointed out.

This strategy has proven successful in the advanced setting. PD-1 inhibitors such as pembrolizumab and nivolumab have achieved significantly high response rates in refractory patients with MSI-high CRC. Clinical trials investigating the use of these drugs in the first-line setting (KEYNOTE-177 and CheckMate 142) have also demonstrated significant benefit.5,6

In the localized setting, the improvements observed in rates of radiographic and endoscopic response with neoadjuvant pembrolizumab compared favorably with, and were sometimes even superior to, the rates in the metastatic setting, noted Ciombor, and further showed the potential for the drug’s use in an organ-sparing treatment strategy.7

Other PD-1 inhibitors that have shown promise for MSI-high CRC include dostarlimab and adjuvant nivolumab and ipilimumab. However, several steps remain to further examine long-term outcomes of these PD-1 inhibitors as an aspect of an organ-sparing approach vs standard-of-care surgery, Ciombor noted.

“We always knew that MSI testing was very important in patients with colorectal cancer, not only to screen for Lynch syndrome, but also in cases of metastatic disease for the potential use of immunotherapy. But now we’re finding that it needs to be tested at any stage and before treatment begins, because this can drastically change how we treat patients,” said Ciombor.

A study is underway at Vanderbilt-Ingram Cancer Center to assess the impact of adjuvant nivolumab/ipilimumab and short-course radiation on complete pathologic response rates of patients with locally advanced rectal cancer who undergo total mesorectal excision.

“It’s really important to get these prospective data, so we know how to change the standard of care in the future," concluded Ciombor.

“We can potentially spare patients from other modalities of therapy in the case of rectal cancer, maybe surgery and radiation. And we need ongoing biomarker studies to understand not only how patients respond, but how long they respond, who doesn’t respond, and the optimal duration of therapy.”

Precision Treatment for Tobacco Use Cessation

Hilary Tindle, MD, MPH, the founding director of the Vanderbilt Center for Tobacco, Addiction and Lifestyle, spoke next, discussing her work regarding precision approaches to tobacco smoking cessation. »
Cigarette smoking is the leading cause of early morbidity and mortality in the United States, and although progress has been made to increase awareness and reduce use of tobacco, about 13% of US adults—30 million individuals—still smoke cigarettes frequently, noted Tindle. This rate is even higher among disproportionately affected groups, such as those living below the poverty line and those residing in the 13 states that have been described as Tobacco Nation, including Alabama, Mississippi, South Carolina, and Tennessee.9

“If you took these states as a country, and compared the smoking rates, it would be fifth worst in the world,” emphasized Tindle. “Many counties in this Tobacco Nation are rural, and there are weaker laws and taxes on cigarettes in some of these states.”

Severe health treatments are available for smoking cessation, such as nicotine replacement, varenicline, and bupropion, but Tindle said that success rates of quitting are relatively low, despite more than half of active smokers trying to quit every year.24

“When medications are used, which is in about a third of all cases in which people try to quit, they’re using a type of one-size-fits-all [strategy]. It’s not done in an informed way that is necessarily tailored to genetics or other important factors,” she said.

Tindle’s work centers around the promise of precision medicine to address these limitations, particularly how nicotine dependence can inform what treatment for smoking cessation is best for each patient. Nicotine dependence, like many other conditions and addictions, is heritable from initiation all the way through cessation, she explained. Hundreds of genetic variants help determine smoking persistence, how much one smokes, and how well smoking-cessation medications fare.

Two chromosomes that influence nicotinic acetylcholine receptors in the brain and nicotine metabolism in the liver have risen to the top in terms of importance, noted Tindle. Right now, nicotine metabolism, a process that can be captured by running a genome-wide association studies analysis, has the most evidence in terms of actionability.

“We can capture nicotine metabolism with just a simple blood, urine, or saliva test, and we can measure the nicotine-metabolite ratio (NMR),” Tindle explained. “That ratio can help us predict how much trouble an individual will have in quitting smoking, and there’s also evidence that it can predict how well a person will do in relation to a certain drug.”

NMR stratifies patients into those with high (fast) or low (slow) nicotine metabolism, she continued. Those with high nicotine metabolism are at greater risk for smoking persistence, intensity and for having more difficulty in quitting smoking, even with treatment.

A clinical trial conducted 7 years ago further showed the utility of the NMR in predicting treatment success. Participating smokers seeking treatment were randomly assigned by baseline NMR status to 11 weeks of placebo, nicotine patch, or varenicline, plus behavioral counseling. After 6 to 12 months, patients who metabolized nicotine faster were found to be approximately twice as likely to quit smoking with varenicline vs nicotine patch, whereas those with slow metabolism showed no difference between the modalities in terms of quitting success. Slow metabolizers, however, experienced significantly more adverse effects with varenicline than with the nicotine patch.

A subsequent clinical trial conducted by Tindle and colleagues demonstrated that most patients seeking smoking cessation treatment would be interested in doing the NMR-based blood test and would follow the recommended strategies based on the results.22 However, a patient’s age, education level, and race could affect their willingness to embrace precision approaches.

“When people are counseled about quitting smoking, sometimes it’s helpful to actually bring in other information, such as what’s your risk of heart disease and lung cancer, and that can actually potentially enhance the conversation and get people motivated or at least help them understand why this is really important,” Tindle added. “Precision medicine is only as good as the foundation of medicine under it.”

Leveraging Genomic Data and Democratizing Precision Oncology

As Vanderbilt-Ingram Cancer Center’s director of cancer clinical informatics, Travis Osterman, DO, MS, plays a key role in interpreting and translating genomic data as they relate to cancer care delivery. He discussed how clinical informatics can optimally support precise diagnosis and individualized treatments.

Although advances in pharmacogenomics have created novel possibilities for personalized care management, Osterman said that these data can prove very complex for clinical teams nationwide. As such, the next step to leverage structured genomic data requires the establishment of data standards to integrate these data into the electronic medical record (EMR) and have clinical decision support.

“I’m going to take the very provocative view that I’m against faxing medical records to me for patient care. I want to receive those records [electronically], just like any other test I order,” he said.

“We had the first group convened to work on a national open-source standard to transmit genomic data in late 2018. At that time, there was one institution in the country that had made a connection to a reference laboratory doing these complex tests receiving that data in a structured format.”

As of 2022, nearly 30 health care systems had adopted the second version of the data standard, the Minimal Common Data Elements initiative, that was released earlier this year. These health systems now receive genomic data from reference laboratories.

“The shift away from the PDFs, faxes, and outside records that proved detrimental to the clinical decision-making process allows for the streamlining of effective care delivery to not only 1 patient, but the entire population of patients cared for at a given cancer center, Osterman said. And over time, the knowledge gained by the expanded use of genomic data can advance precision medicine further on a national and international scale.

“One of the best ways to look at this is as a pipeline….We enter this test in our normal EMR like we normally do. It goes out to a third-party laboratory, which is able to [keep] up with the science benefit and economies of scale. They send us the results back not as a fax, but like any other result internally to our lab that lands in this data set. Then, it’s immediately available to our patients in our patient portal,” explained Osterman.

The availability of these data can allow patients to access findings from their phones and receive second opinions if needed, he said. The data can also help clinicians place patients in groups based on their respective mutations, to match these individuals with clinical trials or effective drugs that best fit their care needs.

Osterman has called for federal guidance over the next decade to address the ethical considerations of genomic data sharing, particularly whether to rerun data from these tests when knowledge about further actionable mutations and targeted treatments enters the oncology pipeline.

“We need to continue to expand genetic/genomic training in medical and nursing schools. These are complex topics,” he said. “Sometimes these get even more complicated when you’re talking about germline testing, where if you have it done once at age 17, that lives with you for the rest of your life.”

Event co-chair Ben Ho Park, MD, PhD, concluded the discussion with thoughts on the advances and challenges that remain in the quest to democratize precision oncology for all patient populations.

As one of the major tools available today to sequence genomic data and interpret health information, NGS has proven effective in matching a patient’s genome sample to a reference and informing clinicians whether it is pathogenic.

However, because these references are an average only of the hundreds of thousands of genome sequences known today, Park said there is still a long way to go in figuring out what is or is not normal—and what is or is not actionable for the 8 billion people living worldwide. Germline genetics is in its infancy in precision oncology, said Park, with only a few companies and institutions incorporating these DNA into tumor sequencing.

“A big problem that many academic centers and communities have is that everyone’s just picking
their own favorite tests or even internal tests. And everyone’s a little bit different in terms of what genes get sequenced so there’s no harmonization of data,” Park said.

“Moreover, you’ll get a portal on the web, and you’ll get some sequences that come in this web portal, some in that portal, none of it really gets automatically integrated in electronic format until Travis and his team come along into our EMRs. As they’ve developed, molecular tumor boards have made progress in assisting clinicians who don’t have adequately deep knowledge of genetics to adjudicate these data in the decision-making process, said Park. Through the REDCap (Research Electronic Data Capture) database, case reports can be uploaded and referenced toward a molecular tumor board, such as the one developed at Vanderbilt-Ingram Cancer Center; results are then uploaded into the EMR.

This has proven to be important for providers, who use this reference when they submit for reimbursement for off-label therapy, said Park, because payers are more likely to approve a therapy that next level, where we …understand the genetic underpinnings of a patient’s cancer, then try to design therapies, or best therapeutic practices, based on that.”

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**REFERENCES**


She needs a treatment shown to reduce risk of recurrence in high-risk early breast cancer (EBC)¹

The first FDA-approved addition to adjuvant ET in nearly 2 decades¹⁻⁹

ET=endocrine therapy; HER2=human epidermal growth factor receptor 2-negative; HR+=hormone receptor-positive.
INDICATION
VERZENIO® (abemaciclib) is indicated in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20% as determined by an FDA-approved test.1

SELECT IMPORTANT SAFETY INFORMATION
Severe diarrhea associated with dehydration and infection occurred in patients treated with Verzenio. Across four clinical trials in 3691 patients, diarrhea occurred in 81 to 90% of patients who received Verzenio. Grade 3 diarrhea occurred in 8 to 20% of patients receiving Verzenio. Most patients experienced diarrhea during the first month of Verzenio treatment. The median time to onset of the first diarrhea event ranged from 6 to 8 days, and the median duration of Grade 2 and Grade 3 diarrhea ranged from 6 to 11 days and 5 to 8 days, respectively. Across trials, 19 to 26% of patients with diarrhea required a Verzenio dose interruption and 13 to 23% required a dose reduction.

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

Neutropenia, including febrile neutropenia and fatal neutropenic sepsis, occurred in patients treated with Verzenio. Across four clinical trials in 3691 patients, neutropenia occurred in 37 to 46% of patients receiving Verzenio. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 19 to 32% of patients receiving Verzenio. Across trials, the median time to first episode of Grade ≥3 neutropenia ranged from 29 to 33 days, and the median duration of Grade ≥3 neutropenia ranged from 11 to 16 days. Febrile neutropenia has been reported in <1% of patients exposed to Verzenio across trials. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

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

Severe, life-threatening, or fatal interstitial lung disease (ILD) or pneumonitis can occur in patients treated with Verzenio and other CDK4/6 inhibitors. In Verzenio-treated patients in EBC (monarchE), 3% of patients experienced ILD or pneumonitis of any grade: 0.4% were Grade 3 or 4 and there was one fatality (0.1%). In Verzenio-treated patients in MBC (MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of Verzenio-treated patients had ILD or pneumonitis of any grade: 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD or pneumonitis have been observed in the postmarketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD or pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations. Dose interruption or dose reduction is recommended in patients who develop persistent or recurrent Grade 2 ILD or pneumonitis. Permanently discontinue Verzenio in all patients with Grade 3 or 4 ILD or pneumonitis.
Verzenio: FDA-APPROVED
for patients with HR+, HER2−,
node-positive EBC at high risk of recurrence and a Ki-67 score ≥20%1-3

APPROVAL BASED ON RESULTS IN PATIENTS WITH THE INDICATED CLINICAL AND PATHOLOGICAL RISK FACTORS (n=2,003)1

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**NODE-POSITIVE DISEASE**

4+ nodes OR 1-3 nodes with
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AND

**Ki-67 ≥20%**

monarchE was a phase III clinical trial that enrolled 5,637 peri- and postmenopausal adult women and men with HR+, HER2−, node-positive EBC at high risk of recurrence. High risk was defined as 4+ positive nodes, or 1-3 positive nodes with Grade 3 disease or tumor size ≥5 cm (central Ki-67 testing was conducted retrospectively for patients with untreated breast tissue samples), or 1-3 positive nodes with Ki-67 ≥20%. All patients completed primary treatment prior to 1:1 randomization to receive either 150-mg, twice-daily Verzenio plus SoC ET or SoC ET alone for 2 years. ET continued through 5-10 years as clinically indicated. The primary endpoint was IDFS.1,2

IDFS=invasive disease-free survival; SoC=standard of care.

**SELECT IMPORTANT SAFETY INFORMATION (cont’d)**

Grade ≥3 increases in alanine aminotransferase (ALT) (2 to 6%) and aspartate aminotransferase (AST) (2 to 3%) were reported in patients receiving Verzenio. Across three clinical trials in 3559 patients (monarchE, MONARCH 2, MONARCH 3), the median time to onset of Grade ≥3 ALT increases ranged from 57 to 87 days and the median time to resolution to Grade <3 was 13 to 14 days. The median time to onset of Grade ≥3 AST increases ranged from 71 to 185 days and the median time to resolution to Grade <3 ranged from 11 to 15 days.

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

Please see Select Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.
Verzenio: The only CDK4 & 6 inhibitor to reduce risk of recurrence in combination with ET\textsuperscript{1,7-9}

*Statistical significance was achieved for this subpopulation earlier at the final IDFS analysis. The result in this post hoc analysis cannot be interpreted as statistically significant.\textsuperscript{1}

At 3 years, Verzenio reduced the risk of recurrence by more than a third\textsuperscript{1}

86.1% of patients remained recurrence-free with Verzenio plus ET vs 79.0% with ET alone.\textsuperscript{1}

The number of events at the time of analysis was 104 with Verzenio plus ET vs 158 with ET alone.\textsuperscript{1}

OS was immature. A total of 95 (4.7%) patients had died. Long-term follow-up is planned.\textsuperscript{1,2}

This post hoc efficacy analysis was performed at a median follow-up of 27.1 months. Additional exploratory analyses were performed at this time; efficacy results for the subpopulation with high-risk clinicopathological features and Ki-67 \(\geq 20\%\) are provided.\textsuperscript{3}

\*HR=hazard ratio; OS=overall survival.

See the breakthrough results at VerzenioData.com/EBC

SELECT IMPORTANT SAFETY INFORMATION (cont’d)

Venous thromboembolic events (VTE) were reported in 2 to 5% of patients across three clinical trials in 3559 patients treated with Verzenio (monarchE, MONARCH 2, MONARCH 3). VTE included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. In clinical trials, deaths due to VTE have been reported in patients treated with Verzenio.

Verzenio has not been studied in patients with early breast cancer who had a history of VTE. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate. Dose interruption is recommended for EBC patients with any grade VTE and for MBC patients with a Grade 3 or 4 VTE.

Verzenio can cause \textit{fetal harm} when administered to a pregnant woman, based on findings from animal studies and the mechanism of action. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with Verzenio and for 3 weeks after the last dose. Based on findings in animals, Verzenio may impair fertility in males of reproductive potential. There are no data on the presence of Verzenio in human milk or its effects on the breastfed child or on milk production. Advise lactating women not to breastfeed during Verzenio treatment and for at least 3 weeks after the last dose because of the potential for serious adverse reactions in breastfed infants.
SELECT IMPORTANT SAFETY INFORMATION (cont’d)

The most common adverse reactions (all grades, ≥10%) observed in monarchE for Verzenio plus tamoxifen or an aromatase inhibitor vs tamoxifen or an aromatase inhibitor, with a difference between arms of ≥2%, were diarrhea (84% vs 9%), infections (51% vs 39%), neutropenia (46% vs 6%), fatigue (41% vs 18%), leukopenia (38% vs 7%), nausea (30% vs 9%), anemia (24% vs 4%), headache (20% vs 15%), vomiting (18% vs 4.6%), stomatitis (14% vs 5%), lymphopenia (14% vs 3%), thrombocytopenia (13% vs 2%), decreased appetite (12% vs 2.4%), ALT increased (12% vs 6%), AST increased (12% vs 5%), dizziness (11% vs 7%), rash (11% vs 4.5%), and alopecia (11% vs 2.7%).

The most frequently reported ≥5% Grade 3 or 4 adverse reaction that occurred in the Verzenio arm vs the tamoxifen or an aromatase inhibitor arm of monarchE were neutropenia (19.6% vs 1%), leukopenia (11% vs <1%), diarrhea (8% vs 0.2%), and lymphopenia (5% vs <1%).

Lab abnormalities (all grades; Grade 3 or 4) for monarchE in ≥10% for Verzenio plus tamoxifen or an aromatase inhibitor with a difference between arms of ≥2% were increased serum creatinine (99% vs 91%; 5% vs <1%), decreased white blood cells (89% vs 28%; 19.1% vs 1.1%), decreased neutrophil count (84% vs 23%; 18.7% vs 1.9%), anemia (68% vs 17%; 1% vs .1%), decreased lymphocyte count (59% vs 24%; 13.2% vs 2.5%), decreased platelet count (37% vs 10%; 9% vs .2%), increased ALT (37% vs 24%; 2.6% vs 1.2%), increased AST (31% vs 18%; 1.6% vs .9%), and hypokalemia (11% vs 3.8%; 1.3% vs 0.2%).

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

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

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

Please see Select Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.

AL HCP ISI_mE 12OCT2021

REFERENCES:
INDICATIONS AND USAGE

Consult the package insert for complete prescribing information.

Venous Thromboembolism

Grade ≥3 of VTE occurred in ≤0.1% of patients receiving VERZENIO. Dose interruption is recommended for early breast cancer patients with any grade VTE. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for advanced or metastatic breast cancer patients with a Grade 3 or 4 venous thromboembolic event.

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

Neutropenia

Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 19% to 32% of patients receiving VERZENIO. Across trials, the median time to the first episode of Grade ≥3 neutropenia ranged from 29 days to 33 days, and the median duration of Grade ≥3 neutropenia ranged from 11 days to 16 days.

Interstitial Lung Disease (ILD) or Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD) or pneumonitis can occur in patients treated with VERZENIO and other CDK4/6 inhibitors. In VERZENIO-treated patients in early breast cancer (monarchE, N=2791), 3% of patients experienced ILD or pneumonitis of any grade: 0.4% were Grade 3 and there was one fatal (0.1%). In VERZENIO-treated patients in advanced or metastatic breast cancer (N=1095): MONARCH 1 (MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of VERZENIO-treated patients had ILD or pneumonitis of any grade: 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD or pneumonitis have been observed in the postmarket setting, with fatalities reported.

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

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

Hepatotoxicity

Grade ≥3 ALT (2% to 6%) and AST (2% to 3%) were reported in patients receiving VERZENIO. Grade ≥3 decrease in ALT or AST occurred more frequently in patients receiving VERZENIO compared with other CDK4/6 inhibitors. Across four clinical trials in 3691 patients, Grade ≥3 decrease in ALT or AST occurred in 0.5% to 2% of patients receiving VERZENIO. Across trials, the median time to the first episode of Grade ≥3 decrease in ALT or AST ranged from 6 to 11 days and 5 to 8 days, respectively. Across trials, 19% to 26% of patients with liver disease required a VERZENIO dose interruption and 13% to 23% required a dose reduction.

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

Monitor electrocardiography (ECG) prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 3 or 4 atrial or ventricular arrhythmias.

Diabetes

Monitor glycosylated hemoglobin (A1C) prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 3 or 4 diabetes.

Neurotoxicity

Grade ≥3 headache occurred in 0.2% to 0.6% of patients receiving VERZENIO. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade ≥3 headache.

Embryo-Fetal Toxicity

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

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

ADVERSE REACTIONS

Clinical Studies Experience

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

The safety population described in the Warnings and Precautions reflect exposure to VERZENIO in 3691 patients from four clinical trials: monarchE, MONARCH 1, MONARCH 2, and MONARCH 3. The safety population includes exposure to VERZENIO as a single agent at 200 mg twice daily in 132 patients in MONARCH 1 and at 150 mg twice daily in 3559 patients administered in combination with fulvestrant, tamoxifen, or an aromatase inhibitor in monarchE, MONARCH 2, and MONARCH 3. The median duration of exposure ranged from 4.5 months in MONARCH 1 to 24 months in monarchE. The most common adverse reactions (incidence ≥20%) across clinical trials were: diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, alopecia, and thrombocytopenia.

Early Breast Cancer

monarchE: VERZENIO in Combination with Tamoxifen or an Aromatase Inhibitor as Adjuvant Treatment

Adult patients with HR-positive, HER2-negative, node-positive early breast cancer at a high risk of recurrence

The safety of VERZENIO was evaluated in monarchE, a study of 5591 adult patients receiving VERZENIO plus endocrine therapy (tamoxifen or an aromatase inhibitor) or endocrine therapy (tamoxifen or an aromatase inhibitor) alone. Patients were randomly assigned to receive 150 mg of VERZENIO orally, twice daily, plus tamoxifen or an aromatase inhibitor, or tamoxifen or an aromatase inhibitor, for two years or until discontinuation criteria were met. The median duration of VERZENIO treatment was 24 months.

The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, leukopenia, diarrhea, and lymphopenia.

Fatal adverse reactions occurred in 0.8% of patients who received VERZENIO plus endocrine therapy (tamoxifen or an aromatase inhibitor), including: cardiac failure (0.1%), cardiac arrest, myocardial infarction, ventricular fibrillation, cerebral hemorrhage, cerebrovascular accident, pneumonitis, hypoxia, diarrhea and mesenteric artery thrombosis (0.03% each).

Permanent VERZENIO treatment discontinuation due to an adverse reaction was reported in 19% of patients receiving VERZENIO, plus tamoxifen or an aromatase inhibitor. Of the patients receiving tamoxifen or an aromatase inhibitor, 1% permanently discontinued due to an adverse reaction. The most common adverse reactions leading to VERZENIO discontinuations were diarrhea (5%), fatigue (2%), and neutropenia (0.5%).

Dose interruption of VERZENIO due to an adverse reaction occurred in 62% of patients receiving VERZENIO plus tamoxifen or aromatase inhibition. Adverse reactions leading to VERZENIO dose interruptions in ≤5% of patients were diarrhea (20%), neutropenia (16%), leukopenia (7%), and fatigue (5%).

Dose reductions of VERZENIO due to an adverse reaction occurred in 44% of patients receiving VERZENIO plus endocrine therapy (tamoxifen or an aromatase inhibitor). Adverse reactions leading to VERZENIO dose reductions in ≤5% were diarrhea (17%), neutropenia (6%), and fatigue (5%).

The most common adverse reactions reported (≥2%) in the VERZENIO, plus tamoxifen or an aromatase inhibitor, arm and ≥2% higher than the tamoxifen or an aromatase inhibitor arm were: diarrhea, infections, neutropenia, fatigue, leukopenia, nausea, anemia, and headache. Adverse reactions are shown in Table 1 and laboratory abnormalities are shown in Table 2.

Table 1: Adverse Reactions (≥10%) of Patients Receiving VERZENIO Plus Tamoxifen or an Aromatase Inhibitor (with a Difference between Arms of ≥2%) in monarchE

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>VERZENIO Plus Tamoxifen or an Aromatase Inhibitor N=2791</th>
<th>All Gradesa</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Gradesa</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>84</td>
<td>8</td>
<td>0</td>
<td>9</td>
<td>0.2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
<td>0.5</td>
<td>0</td>
<td>9</td>
<td>&lt;0.1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>0.5</td>
<td>0</td>
<td>4.6</td>
<td>0.1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>14</td>
<td>0.1</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infections and Infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectionsb</td>
<td>31</td>
<td>4.9</td>
<td>0.6</td>
<td>39</td>
<td>2.7</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatiguec</td>
<td>41</td>
<td>2.9</td>
<td>0</td>
<td>18</td>
<td>0.1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>20</td>
<td>0.3</td>
<td>0</td>
<td>15</td>
<td>0.2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>0.1</td>
<td>0</td>
<td>7</td>
<td>&lt;0.1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>0.6</td>
<td>0</td>
<td>2.4</td>
<td>&lt;0.1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

VERZENIO® (abemaciclib) tablets, for oral use

VERZENIO® (abemaciclib) tablets, for oral use
TABLE 1: Adverse Reactions (≥10%) of Patients Receiving VERZENIO Plus Tannoxifen or an Aromatase Inhibitor (with a Difference Between Arms of ≥2%) in monarchE (Cont.)

<table>
<thead>
<tr>
<th></th>
<th>VERZENIO Plus Tannoxifen or an Aromatase Inhibitor</th>
<th>Tannoxifen or an Aromatase Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades*</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>27</td>
<td>0</td>
</tr>
</tbody>
</table>

- Includes the following fatal adverse reactions: diarrhea (n=1), and infections (n=4)
- Includes mouth ulceration, mucosal inflammation, oropharyngeal pain, stomatitis.
- Includes all reported preferred terms that are part of the Infections and Infestations system organ class. Must common infections (≥5%) include upper respiratory tract infection, urinary tract infection, and nasopharyngitis.
- Includes asthenia, fatigue.
- Includes exfoliative rash, mucocutaneous rash, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash maculovesicular, rash morbilliform, rash papular, rash papulosquamous, rash pruritic, rash vesicular, urticarial rash.

Clinically relevant adverse reactions in <10% of patients who received VERZENIO in combination with tamoxifen or an aromatase inhibitor in monarchE include:
- Pruritus-9%
- Dyspepsia-8%
- Nail disorder-9% (includes nail bed disorder, nail bed inflammation, nail discoloration, nail disorder, nail dystrophy, nail pigmentation, nail ridging, nail toxicity, onychia, onycholysis, onychotaxis, onychomadesis)
- Laceration increased-6%
- Dyspepsia-5%
- Intestinal lung disease, pulmonary fibrosis, organizing pneumonia, radiation fibrosis – lung, lung opacity, sarcoidosis)
- Venous thromboembolic events (VTEs-3% (includes catheter site thrombosis, cerebral venous thrombosis, deep vein thrombosis, device related thrombosis, embolism, hepatic vein thrombosis, jugular vein occlusion, jugular vein thrombosis, ovarian vein thrombosis, portal vein thrombosis, pulmonary embolism, subclavian vein thrombosis, venous thrombosis limb)

TABLE 2: Laboratory Abnormalities (≥10%) in Patients Receiving VERZENIO Plus Tannoxifen or an Aromatase Inhibitor (with a Difference Between Arms of ≥2%) in monarchE

<table>
<thead>
<tr>
<th></th>
<th>VERZENIO Plus Tannoxifen or an Aromatase Inhibitor</th>
<th>Tannoxifen or an Aromatase Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades*</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>99</td>
<td>0.5</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>89</td>
<td>19</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>84</td>
<td>14</td>
</tr>
<tr>
<td>Anemia</td>
<td>68</td>
<td>1.0</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>59</td>
<td>13</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>37</td>
<td>0.7</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>37</td>
<td>2.5</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>31</td>
<td>1.5</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>11</td>
<td>1.2</td>
</tr>
</tbody>
</table>

**DRUG INTERACTIONS**

**Effect of Other Drugs on VERZENIO**

CYP3A Inhibitors

Strong and moderate CYP3A4 inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity.

Ketoconazole

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

Other Strong CYP3A Inhibitors

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

Moderate CYP3A Inhibitors

With concomitant use of moderate CYP3A4 inhibitors, monitor for adverse reactions and consider reducing the VERZENIO dose in 50 mg decrements, if necessary.

Strong and Moderate CYP3A Inducers

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

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

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

**Data**

**Animal Data**

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

**Lactation**

**Risk Summary**

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

**Females and Males of Reproductive Potential**

Based on animal studies, VERZENIO can cause fetal harm when administered to a pregnant woman.

**Pregnancy Testing**

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

**Contraception**

Females

Advise females of reproductive potential to use effective contraception during VERZENIO treatment and for 3 weeks after the last dose.

**Infertility**

**Males**

Based on findings in animals, VERZENIO may impair fertility in males of reproductive potential.

**Pediatric Use**

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

**Geriatric Use**

Of the 2791 VERZENIO-treated patients in monarchE, 15% were 65 years of age or older and 2.7% were 75 years of age or older.

Of the 900 patients who received VERZENIO in MONARCH 1, MONARCH 2, and MONARCH 3, 38% were 65 years of age or older and 10% were 75 years of age or older. The most common adverse reactions (≥5%) Grade 3 or 4 in patients ≥65 years of age across MONARCH 1, 2, and 3 were: neutropenia, diarrhea, fatigue, nausea, dehydration, leukopenia, anemia, infections, and ALT increased.

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

**Renal Impairment**

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

**Hepatic Impairment**

No dosage adjustments are necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B).

Reduce the dosing frequency when administering VERZENIO to patients with severe hepatic impairment (Child-Pugh C).

Additional information can be found at [www.verzenio.com](http://www.verzenio.com)
Ochsner Health’s Chemotherapy Care Companion Reduces Hospital Visits, Drives Patient Satisfaction

OCHSNER HEALTH’S REMOTE monitoring system for patients receiving cancer treatments helped drive down hospital stays and emergency department (ED) visits by one-third while improving patient satisfaction among those who used the service, according to a physician who led the project.

Zoe Larned, MD, system chair of hematology and oncology for Ochsner, outlined the development of the system, called Chemotherapy Care Companion, and shared early results during a session of the Association of Community Cancer Centers (ACCC) 39th National Oncology Conference held in West Palm Beach, Florida. Ochsner’s program was among the recipients of the 2022 ACCC Innovator Awards, given to projects that improve patient care and are cost-effective and replicable.1

In January 2020, creating a digital health system to monitor patients with cancer between office visits was a natural next step for the Ochsner Cancer Institute, which had already embedded urgent care slots within its oncology clinics starting in 2018, Larned explained. Little did Ochsner know how vital remote monitoring would become, when the COVID-19 pandemic gave added value to the ability to remotely track patients’ blood pressure, temperature, pulse, and weight, as well as responses to questions about symptoms.

“The rationale for doing more with monitoring processes in cancer care is that [this is] a health care delivery method that uses technology to allow us to monitor patients outside of the clinical setting and between visits,” Larned said.

This is especially important in cancer care, she explained. Although advances in systemic cancer therapies offer substantial benefits, they can also come with significant toxicity. The ability to use technology to record patient metrics and symptoms remotely means “we’re able to continue to monitor them in ways that we have not historically been able to do before.”

Larned said that 27% of patients with solid tumors have at least 1 visit to the ED during their treatment course; patients with hematologic malignancies often start treatment in the hospital.

Ochsner’s system is designed to flag signs of the top reasons for admission or an ED visit: infection and sepsis, dehydration, pain, and hypertension. The system, launched at Ochsner Cancer Institute in New Orleans, Louisiana, called for patients to enroll through a smartphone or iPad app, where they provided consent and information, and for the health system to provide them with a blood pressure cuff, ear thermometer, and digital scale. Patients were asked to record their metrics and answer questions twice a day, in the early morning and midafternoon, which would give care teams time to see which patients were showing signs of dehydration or infection or were reporting adverse effects (AEs) from medication. If a patient needed an urgent care visit, those slots were already built into the schedule.

Larned’s presentation included screenshots of what the enrollment process looks like on an electronic health record and how seamlessly it fits into the workflow. Patients newly prescribed chemotherapy were automatically workflow. Patients newly prescribed chemotherapy were automatically

enrolled, and Ochsner has since added in those patients already receiving therapy for cancer. And despite the name, those taking oral therapies or immunotherapy are also included—and may stay enrolled after their regimen ends due to the nature of AEs.

RESULTS. Preliminary data collected from January 2020 through December 2021 showed that patients who participated in the digital monitoring program had a 33% reduction in ED visits and hospital admissions compared with those who were not enrolled.

As of today, Larned said, 500 patients have enrolled in the program, ranging in age from 23 to 86 years. Adherence to the program is 70%; Ochsner considers a patient adherent if they complete at least half of the assigned daily tasks.

Although 50% of the patients enrolled have stage IV cancer, Larned said the program has monitored patients at every stage—and she is optimistic about its usefulness in patients with earlier-stage cancers. “We know if we can monitor patients between appointments, it’s just as important to get our [patients at] earlier stages enrolled,” she said.

Since its launch, Chemotherapy Care Companion has expanded from Ochsner’s flagship center to its regional cancer centers and clinic sites, which stretch from northern Louisiana in Shreveport to the Mississippi Gulf Coast. Ochsner leaders have refined the system to shut off if a patient is admitted to the hospital and have adapted the baseline measures to acknowledge that Louisiana’s overall health status is poor compared with other states. (Separately, Ochsner is leading a statewide effort to raise Louisiana’s health measures by 2030.)

Chemotherapy Care Companion is not considered optional at this point, Larned explained. “We’ve made this a value-based metric for our team. All providers have bought in as part of our value-based measures.”

REFERENCE

Delaware’s ChristianaCare Embeds PCP Care Within the Cancer Center

WITH PATIENTS WHO HAVE CANCER living longer, it’s more important than ever to build connections between the oncologist and the primary care provider (PCP) who will take care of a patient’s health needs beyond cancer.

But what happens if the patient with cancer has no PCP? This was the challenge that ChristianaCare’s Helen F. Graham Cancer Center and Research Institute, based in Newark, Delaware, took on when it embedded PCP care within the cancer center, both to provide for the immediate needs of the center’s patients and to connect them with primary care for the future.

ChristianaCare is the dominant health care system in Delaware, the nation’s second-smallest state, with 3 hospitals including a Level 1 trauma center.1 But, as Debra Delaney, MSN, FNP-BC, primary care nurse practitioner, explained during the Association of Community Cancer Centers (ACCC) 39th National Oncology Conference, held in West Palm Beach, Florida, Delaware’s»
smallest can still mean long drives for some residents in the most rural stretches of the state. ChristianaCare's program was among the winners of the 2022 ACCC Innovator Awards.2

Delaneys shortage of PCPs is acute, meaning that ChristianaCare was seeing more and more patients with cancer who had no family practice to rely on outside of cancer treatment. An estimated 15% of the cancer center's gynecological oncology patients had no PCP for example. That meant they had no other physician to help manage comorbidities or deal with care coordination, which led to treatment delays and unnecessary stress.

When the idea was presented to Delaney to embed PCP care at the cancer center, she knew it made perfect sense. "Everyone should have a PCP, but we know thats not the case," she said.

The launch of PCP care in the cancer center took flight in January 2021, with a small unit of 5 beds, advanced practice clinicians, a registered nurse, and a medical office assistant. Delaney also sees some patients via telehealth. Within 6 months, there were 70 patients, she said.

In a year's time, ChristianaCare has learned a lot. "Its a constantly evolving practice," Delaney explained. The original plan was to set up a referral to primary care as soon as treatment ended, but the cancer center soon found that more challenging than expected. Patients might end up going to the emergency department if they dont have a PCP, if a suspicious mass is found or a new issue arises, they are referred back. Patients who need presurgical evaluations and have no PCP are also referred.

And there are advantages to being embedded in the cancer center, Delaney said. Access to each patients cancer records is a huge advantage, as she can see all the notes; she described how being part of the cancer center offered access to information that prevented her from prescribing a diarrhea medication that would have interfered with a patients clinical trial. In another case, the oncologist had explained which medications were contraindicated with cancer therapies, including one that was not obvious.

Still, its part of Delaneys job to ultimately connect patients with local PCPs when possible, and she spoke of those successes, too. She manages the timing of the handoff back to a local provider and helps patients find one when possible. "If youve got patients [who] travel over 2 hours from downtown they prefer to have a primary care provider that [is] closer to their home, which I can certainly help with," she said.

When these handoffs occur, Delaney ensures that the new provider has all the patients data and fully understands the case.

And there are a few patients who resist a transfer, even when its in their interest. Delaney reviewed the case of a veteran who found the Veterans Affairs Health Care System very complex, but the cancer center worked with him on a transition so he could access a host of social supports for which he was eligible. "I sat down with him, and we had a long talk about this," she said. When the veteran was able to make the transition, "he was very grateful."

**ORAL ONCOLYTIC DELIVERY.** Baptist Health South Floridas Miami Cancer Institute had a problem. The rise of oral oncolytics in cancer care, staffing challenges, COVID-19, and processes that clinicians used to manage prior approval challenges had all combined to create barriers to patient medication education.

An audit had revealed a major gap: Miami Cancer Institute offered high-quality education, but it wasnt always timely. With problems such as while bagging increasing, only about 60% of patients received a prescription and an education session in the same visit. That meant there was a risk that some would start taking oral oncolytics before their education session.

Morgan Nestingen, MSN, APRN, AGNCS-BC, NEA-BC, OCN, ONN-CG, director of nursing for Patient Intake and Navigation Services, explained both the commitment and the process that led to same-day education, which earned Miami Cancer Institute a 2022 ACCC Innovator Award.2

Nestingen admitted that some were skeptical that the goal of same-day education delivery could be achieved. Prior authorization had bedeviled physiciansand it was driving prescribing practices, she said.

The plan involved creation of a dashboard that would measure compliance by capturing orders on the electronic health record and following through to ensure that navigators and nurses had the opportunity to complete all necessary steps to educate patients on the medication they would be taking while they were on site. Innovative technology allowed for electronic consent, and on-call nursing support is part of the equation. It took plenty of 7 AM Friday meetings, support from information technology staff, and "a lot of microadjustments" to make minor changes that added up to a big shift.

By the second month of the project, same-day compliance had reached 90%; by the end of month 3, it had reached 95%. The project is now heading into a second phase, she said. The lesson, Nestingen emphasized, is that "technology can enhance traditional approaches to in-person care coordination." •

**REFERENCES**


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**Allina Health: Bringing Population Health Strategies to Oncology**

**THREE YEARS AGO.** Allina Health, a not-for-profit health system that operates 10 hospitals and more than 90 clinics in Minnesota and western Wisconsin, decided to invest in cancer care with a population health focus. Doing so required Allina to "remap the patient experience" in cancer care, according to Mike Koroscik, MBA, MHA, vice president of oncology at Allina Health Cancer Institute (AHCI).

Koroscik offered an update on how that process has evolved for AHCI, which launched in October 2021.1 Koroscik presented "Preparing for Population Health in Oncology" during the Association of Community Cancer Centers 39th National Oncology Conference, which was held in West Palm Beach, Florida.

His talk added to the emerging consensus that improving patient experience and bringing down cancer costs calls for prevention through healthier living or catching cancer early when it is easier and less expensive to treat. The second approach requires using data and risk stratification strategies to screen patients and to rethink reimbursement, which would have to reward health systems based on a population health model rather than paying for testing based on individual patient risk.

Koroscik began by discussing why population health in oncology is in vogue. Although Allina made its commitment before the pandemic, COVID-19 highlighted the enormous need for a population health approach, and the "silver linings" of that experience are fueling some of AHCI's early steps.

"Cancer care was disjointed," Koroscik said. "Even mapping our largest cancer type—breast cancer—had over 33 touch points before the AHCI overhaul began. Clearly, an intervention that revamped the traditional hub-and-spoke relationship between flagship and rural sites had to be rebuilt.

"We knew our value proposition was redefining cancer care, making it accessible," he said. "We had to focus on a new network."

In August 2020, Allina Health reached an agreement on what was described as a "landmark" value-based contract with Blue Cross and Blue Shield of Minnesota, 2 and Koroscik said larger payers are the focus of AHCI's efforts in value-based care.
From there, he said the AHCI model would be one of accessible “seamless connections” that recognizes the multiple factors—mind, body, and spirit—that affect overall health. The model includes the following components:

- Integration of primary care and mental health
- A patient financial navigation program that addresses financial toxicity
- Exceeding expectations on screening and surveillance
- Convenient hours and availability of urgent care, to reduce emergency department (ED) visits and hospital admissions
- Better utilization of nurse navigators, "to thrive, not just survive" under bundled payment arrangements
- Upfront engagement of payers in innovative population health initiatives, which include social and community-based initiatives

LESSONS FROM COVID-19. The sharp drop in cancer screening that took place in the early months of the pandemic—and the resulting cancers that followed—build the case for an emphasis on preventive care and addressing social needs. "The numbers were devastating," Koroscik said.

But building a patient-centered, population health–focused oncology model necessarily "depends on finding a sustainable path forward," Koroscik said, so cost control is part of the picture. At the macro level, that means building a model centered on providing evidence-based care, minimizing care variation, and paying attention to the total cost of care. Other interventions will focus on the following:

- Reducing acute care crises
- Ensuring fewer ED visits and hospital admissions, and reducing length of stay
- Improving care transitions and care management
- Selecting the appropriate site of care, including home care where appropriate

To support its value-based agreements, Allina Health will rely on informatics support that goes beyond traditional pathways toward more real-time assessment and better panel management.

Typical characteristics of value-based care agreements are benchmarks based on the total cost of care, shared savings, and pay-for-performance metrics. Adding population health to oncology care will put more focus on risk adjustment, Koroscik said. Palliative care will continue to gain attention, as will minimizing unnecessary variation in care.

To support these agreements, Allina Health will rely on informatics support that goes beyond traditional pathways toward more real-time assessment and better panel management. Koroscik reviewed the elements that go into a composite risk score, which is a metric and decision tool that reflects the urgency of the patient’s situation, the depth of clinical need, financial risk, social determinants of health, and likelihood of adherence.

"For us, this is a real game changer," he said. This is where Allina Health can change incentives for physicians to align with quality targets, reduce variation, and improve outcomes.

Current areas of focus are ED avoidance, clinical pathways (medical, radiation, and surgical), shifting symptom management near the infusion center, the home hospital program, lung cancer screening, and encouraging serious illness conversations. Looking ahead, Koroscik is mindful of what is coming from the CMS in alternative payment models (APMs), including the long-delayed Radiation Oncology Model that will likely reduce payments. Gathering data now is essential to be ready for when the APM arrives, he said.

Allina Health is trying new things: 18,000 patients have been screened as part of a social vulnerability pilot, and Koroscik said there are programs for lesbian, gay, bisexual, transgender, and queer populations and for Minnesota's Somali community.

In Allina's work with payers, he said, it's important to keep in mind that "bundles might be good, or they might not be good," depending on the population.

What’s critical is data. Even getting a basic measure such as how many patients have accessed the ED at 30 days isn’t always simple.

"Only 10 years ago I was data starved," Koroscik said. "I don't have too much data, but it's getting the right data.”

REFERENCES

City of Hope: Adapting Pharmacy Roles With an Eye Toward Retention

THE "GREAT RESIGNATION" has hit institutions large and small, and even one of the nation's leading cancer research and treatment centers is not immune.

So, when City of Hope National Medical Center, centered in Duarte, California, found itself struggling to attract and retain clinical pharmacists, a rethinking of their role was in order, according to Wafa Samara, PharmD, chief pharmacy officer, City of Hope Pharmacy Enterprise, and Sepideh Shayani, PharmD, BCOP, executive director of pharmacy enterprise, City of Hope Pharmacy Enterprise.

Samara and Shayani offered an overview of how City of Hope tackled its pharmacy retention challenge during the Association of Community Cancer Centers 39th National Oncology Conference, which was held in West Palm Beach, Florida. Several sessions that day focused on staffing issues, which attendees identified as a top problem during a session held the day prior.

Samara introduced the audience to City of Hope's 100-year-old history and mission; the health system, now expanded beyond its southern California base, is a National Cancer Institute-designated Comprehensive Cancer Center and part of the National Comprehensive Cancer Network. It attracts top talent to be sure—it's scientists have pioneered advances in stem cell transplants and chimeric antigen receptor T-cell therapy.

But as Shayani noted, all that requires the work of 250 oncology clinical pharmacists, and "they are a rare breed."

"What we have been seeing over [the] past several years is a trend of highly trained pharmacists making a decision to choose alternate career paths—not always in patient care," Shayani added.

City of Hope, she said, "recognized a need for us to optimize our patient care model" to allow pharmacists to work at the top of their license and, where possible, to engage in clinical activities—work that keeps pharmacists engaged and retains them. »
This would require an overhaul of the pharmacy department structure, which Shayani described as “a beautiful challenge for us.”

City of Hope hires both clinical pharmacists and pharmacy technicians; the former can work in clinical activities or in operations, which involves administrative work and making medicines. The titles of most of these staff did not truly reflect the scope of their duties, she said.

In addition, City of Hope looked to research by the University of North Carolina on oncology pharmacists in academic medical centers; 44% of the respondents had been in their roles for at least 5 years, and 21% had been in their jobs for 10 years. The research found that 60% of these staff were open to alternative careers, and 23% were at high risk for attrition, meaning they were actively looking for a different job.

Notably, the survey found that clinical work increased job satisfaction and made pharmacists less likely to leave—a result consistent with what City of Hope had observed.

So, how could City of Hope respond? Samara outlined a road map for change, recognizing that “changing culture and care models is not a one-time event.”

- Step 1 was a gap analysis, which looked at how other organizations managed their oncology pharmacists.
- Step 2 created a new career ladder with more distinct job descriptions and responsibilities; those who wanted to remain in operational titles could do so, but those who wanted to focus on clinical activities could move into newly created titles.
- Step 3 involved communicating the restructuring plan to all stakeholders and getting the resources to make it work. This also involved creating pathways for internal staff to shift jobs. Some new hires would be needed.
- Step 4 will implement the restructuring plan, and this “will go on for a long time,” Samara said.

Many elements are needed for restructuring to work, Shayani said. Besides creating new titles for the staff, City of Hope redeployed the numbers in ambulatory and inpatient areas and used technology to streamline operations so that inpatient pharmacists could be with patients.

Collaborative practice agreements, which are permitted by California’s licensing board, allow pharmacists to prescribe medications and manage patients under certain conditions. This has opened the door for pharmacists to manage clinics and run point on a host of items, from oversight of medication toxicity to management of oral therapies to dose adjustments and billing where appropriate. Pharmacists have taken on a medical oncology head and neck clinic and a multiple myeloma clinic, for example.

Working to the top of their license has allowed pharmacists to take on tasks such as handling transitions of care in an allogenic stem cell transplant clinic and has provided opportunities to take greater roles in clinical research, including presentations at conferences. It has also created opportunities for flexibility for work-from-home scheduling, Shayani said, which has helped City of Hope meet the needs of parents with young children.

Finally, Samara said, the process has also allowed City of Hope to examine how it can improve the diversity of its workforce. “We did not match the community we serve,” she said. An internship program that brought in students from underrepresented communities—on salary and with housing support—has just graduated its first cohort, she said; the hope is that these students will become future applicants for the residency program.

Samara said there are many lessons from the experience: “For us, we are successful because we got leadership buy-in.” That meant the process received support throughout from the information technology staff and other resources.

But staff engagement and culture change remain the biggest challenge. City of Hope held town hall meetings so that pharmacists would understand, “What’s in it for me?” And leadership must accept that some pharmacists will still leave, while others will stay.

“"This is a journey, and we need to [be] nimble,” Samara said. “We need to be ready to change and tweak as we go.”

REFERENCE


Understanding the Complexity of Oncology Drug Pricing

THE EXPLOSION OF NEW, lifesaving therapies in oncology offers opportunities to transform patients’ lives. But for some, the complex system of pricing, insurance coverage, and rebates in the United States creates barriers to care, according to an expert who spoke during the Community Oncology Alliance Payer Exchange Summit in Tyson's Corner, Virginia.

Brian Corvino, MBA, managing director of life sciences and health care practice, Deloitte Consulting, LLP, offered an overview of how the surge of innovation in oncology—and resulting drug approvals—is dominating the biopharmaceutical sector. As he noted, new therapies, better screening and prevention, and other improvements have led to a 32% drop in cancer death rates during the past 3 decades, alongside a 73% rise in survival gains.

For many patients, the focus has shifted to survivorship; some may take medication over an extended period. “If you think about how different that is from the insurance benefit designs of many years ago—in certain cancer conditions we are really moving toward normal chronic disease management,” Corvino said.

The rise of FDA approvals in oncology, including a bumper crop in 2021, “has come with greater focus on precision medicine and biomarker-driven trials, he said. Most approvals occur through expedited pathways, which Corvino noted require ongoing studies and investment after the approval.

Oncology, by far, outpaces other disease areas for research and development into new therapies. “This has been the frontier,” Corvino said, where the smartest scientists go to spend their careers. Yet, as has been well documented, for every success in drug development, there are many failures—the success rate is approximately 10%.

DRUG PRICING AND VALUE. Once approved, a cancer therapy must get to patients, and Corvino explained that this is far from a direct path. He described a drug’s journey through “an ecosystem” that includes payers and pharmacy benefit managers (PBMs), employer groups, pharmacies, distributors, pathway vendors, provider groups, and population health decision makers, among others. A PBM decision tree looks like a subway system map before one lands at what seems a simple question: What does a drug cost?

As Corvino explained, this question has many answers. The “price” of a drug is defined many ways, depending on the stakeholder and where the drug is on its path to the patient. For example, wholesale acquisition cost (WAC) is not the same as average sales price (ASP), yet both are important in other parts of the ecosystem, with ASP being used to calculate reimbursement for providers.

Corvino said there is more than 1 “lens” to consider when establishing the WAC. Beyond traditional market considerations, the new Inflation Reduction Act offers new guidance on thinking about costs, as it spells out terms that...
Drug makers use multiple factors to set prices, including measures of value—such as quality-adjusted life years, and whether the drug’s use yields net savings, such as reducing overall hospital admissions.

Second, Corvino explored the reality of net prices in drug spending. Although spending has increased by $82 billion in the past 5 years, he said the main drivers have been the number of new drug brands and their volume, not the prices. These factors were offset by the arrival of generics, as older brands lost exclusivity and gave patients lower-priced options. Although overall oncology drug spending is projected to climb to $114 billion by 2026, growth will slow due to uptake of biosimilars, and Corvino projected that drug spending as a percentage of health spending is “roughly comparable, if not slightly below the average.”

Drug makers use multiple factors to set prices, including measures of value. These include traditional measures such as quality-adjusted life years, and whether the drug’s use yields net savings, such as reducing overall hospital admissions.

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**Redesigning Benefits, Value-Based Agreements With Better Cancer Care in Mind**

**TO DELIVER BETTER CANCER CARE** and save money, some employers have turned to direct contracting. In some places, practices that are too small for the Oncology Care Model (OCM) have tried adjustable care coordination fees. Even before the OCM, larger practices brokered agreements with insurers to deliver value-based care, and those agreements remain today.

Lalan Wilfong, MD, vice president of payer relations and practice transformation, The US Oncology Network, led the discussion, “New Strategies for Insurance Benefit Designs: From the Simple to the Complex,” which examined how employers can reduce the cost of cancer care—sometimes by thousands of dollars. Joining Wilfong were:

- Bret Jackson, president, Economic Alliance for Michigan;
- Pete Scruggs, principal, Golsan Scruggs Insurance & Risk Management, and founder, benefitSmart Cancer Solutions; and
- Karen van Caulil, PhD, president and CEO, Florida Alliance for Healthcare Value.

Wilfong asked for an overview of the market, and van Caulil said that as the COVID-19 pandemic eases, there is renewed interest in cancer care among employers. A recent survey showed that cancer had surpassed musculoskeletal conditions as the top area of benefit spending, she said. Finally, van Caulil said, plan designs are embracing the concept of precision medicine by paying for biomarker testing and targeted therapies. “They’re finally seeing the value of paying for that on the front end.”

Attention to mental health in cancer care and high-value providers are other trends, she said.

Jackson’s coalition is evenly split between companies and labor unions, and many employees have rich benefit plans where cost sharing is not top of mind for hourly employees. The focus since 2017 has been on creating incentives for oncologists to stick with evidence-based medicine based on National Comprehensive Cancer Network guidelines, in part by reducing administrative burdens if practices can provide data that show guideline adherence.

Scruggs, who serves the Portland, Oregon, and southwest Washington State markets, outlined a direct contracting program developed with employers in those areas that he is trying to bring to all 50 states. “It’s a massive savings...”
for these employers," Scruggs said, often 50% of the cost of treatment that had been $100,000; for higher-cost drugs such as pembrolizumab, the savings are larger.

Typically, he said, this level of savings allows the employer to eliminate cost sharing for patients, who are likely already missing time from work and opportunities for raises or bonuses. Recent evidence shows that patients experiencing financial toxicity are less likely to stick with their medication regimen; thus, removing these burdens can improve outcomes.

INSURER PERSPECTIVES. Michael Diaz, MD, president and managing physician of Florida Cancer Specialists & Research Institute (FCS), led the next panel, “Insurer Perspectives on Oncology Reform Efforts and New Payment Models,” which featured:

• René Frick, senior director, Network Innovation & Partnerships, BlueCross BlueShield (BCBS) of South Carolina;
• Stacie Mason, provider partner principal, Provider Relations, BCBS of Minnesota; and
• Ray Parzik, senior director, Value Based Contracting, Florida Blue.

Frick repeated a warning heard throughout the COA Payer Exchange Summit: Some value-based models, including those unveiled by the Center for Medicare and Medicaid Innovation (CMMI), may be too risky for small practices that are already missing time from work and opportunities for raises or bonuses. Recent evidence shows that patients experiencing financial toxicity are less likely to stick with their medication regimen; thus, removing these burdens can improve outcomes.

The CMMI encouraged commercial plan participation in the OCM, and Frick said that BCBS of South Carolina was able to adjust its model, “but we didn’t do shared savings.”

Today, she explained, the insurer’s partnerships with practices revolve around monthly care coordination fees, which can rise or fall at predetermined intervals based on both internal benchmarks and comparisons to peer practices. Ten practices participate and are evaluated based on 6 cancer types every 6 months, Frick said. Mason said Minnesota Oncology asked BCBS of Minnesota to enter a value-based arrangement, which took a few years to complete. Like the South Carolina agreement, the agreement covers care coordination—in this case, for both commercial and Medicare Advantage. It has both fee-for-service and total cost of care components. As Mason explained, the agreement covers 2 distinct types of risk scenarios and spells out the conditions for shared savings.

“As is the case in South Carolina, there are elements for data sharing, which helps BCBS of Minnesota with vendor selection and quality measurement. But there remain elements that are challenging to reconcile.”

“We believe this is a learning opportunity for both of us,” Mason said. “We’ve seen this relationship as something that will evolve over time, and so we are working together to see what works.”

Frick was candid that BCBS of South Carolina applied for the EOM largely at the urging of Kashyap Patel, MD, the current COA president who is CEO of Carolina Blood and Cancer Care Associates, a small practice based in Rock Hill, South Carolina. The insurer’s relationship with Patel is clearly a component in its willingness to explore the workability of the EOM, despite concerns about the model’s reporting requirements.

Parzik traced the history of Florida Blue’s foray into value-based oncology agreements, which started with the “just do it” mentality of CEO Patrick Geraghty in 2010 and led to the first agreement with Advanced Medical Specialties of South Florida. From there, Florida Blue executed dozens of agreements, learning more about what worked. The agreement with FCS, reached in 2016, marked a milestone in the plan’s design. The 2 sides announced an update earlier this year that found an 18% reduction in health care spending and a 22% decline in emergency department visits in the agreement’s fourth year.

Over time, Parzik said, the FCS agreement added measures of downside risk. “When we did it in a thoughtful way, we were well aware that downside risk is not a one-size-fits-all approach,” Parzik said. Independent oncologists and hospitals do not have the same structures for taking on risk, and this must be recognized. He said the need for a “collaborative spirit” is essential to take on any such agreement—there must be trust when the 2 sides are sharing data bidirectionally and working to understand complex issues in cancer staging and genomics.

“We want to make sure what we’re doing is accurate and fair,” he said.

Mason agreed that trust is essential for insurers to pursue agreements with practices. “It’s important that it be something that where you have a partner, and you are willing to take leaps together, to be honest to lay your cards on the table,” she said. “That’s really, really important.”

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Cancer Payment Models Improve Care, but Making Them Work Takes Effort

VALUE-BASED PAYMENT MODELS in cancer care have done much to improve outcomes and patient experience, and over time they can have positive effects on practice culture. But making the models work financially is painstaking, according to 3 practice leaders who discussed what it takes during the Community Oncology Alliance Payer Exchange Summit, held in Tyson’s Corner, Virginia.

Michael Diaz, MD, president and managing physician, Florida Cancer Specialists & Research Institute, served as moderator for the discussion, “Cancer Care Team Perspectives on Oncology Reform Efforts and New Payment Models,” which featured:

• David Cosgrove, MD, medical director, Compass Oncology, which serves patients in the Portland, Oregon, and Vancouver, Washington, areas; and
• Scott Kruger, MD, FACP, medical director, Virginia Oncology Associates, of Hampton Roads; and
• Aaron Lyss, MBA, senior director, payment and policy innovation, OneOncology, which serves 15 practices nationwide from its base in Nashville, Tennessee.

Diaz encouraged the panelists to share what has gone well with value-based care and, later, what has proved frustrating. Cosgrove said that Medicare's
In the treatment of newly diagnosed, transplant-ineligible multiple myeloma:\footnote{1}

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\[ HR=0.68; 95\% CI: 0.53, 0.86; P=0.0013; mOS not reached in either arm. \]  

\*Median follow-up was 56 months in the DRd group (range: 53.0–60.1 months) and in the Rd group (range: 52.5–59.4 months).\footnote{1,**}

DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); mOS=median overall survival; Rd=lenalidomide (R) + dexamethasone (d).

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**IMPORTANT SAFETY INFORMATION**

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DARZALEX® can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening, and fatal outcomes have been reported. In clinical trials (monotherapy and combination; N=2066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX®. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma.

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Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting, and nausea. Less common signs and symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision.

When DARZALEX® dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX®, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX® following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4; <1%) with those reported in previous studies at Week 2 or subsequent infusions. In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days, i.e., 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 14% on Day 2 of Week 1, and 8% with subsequent infusions.

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- 66% of patients were still alive with DRd vs 53% with Rd alone (DRd: 95% CI, 60.8–71.3; Rd: 95% CI, 47.2–58.6).

| Median follow-up was 56 months. Median OS was not reached for either arm |

| 32% reduction in the risk of death in patients treated in the DRd arm vs Rd alone (HR=0.68; 95% CI: 0.53, 0.86; P=0.0013) |

Demonstrated safety profile

(median treatment duration of 25.3 months)

The most common adverse reactions (≥20%) for DRd were diarrhea, constipation, nausea, vomiting, upper respiratory tract infection, bronchitis, pneumonia, infusion-related reactions, peripheral edema, fatigue, asthenia, pyrexia, back pain, muscle spasms, dyspnea, cough, peripheral sensory neuropathy, and decreased appetite.

Serious adverse reactions with a 2% greater incidence in the DRd arm compared with the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%).

IMPORTANT SAFETY INFORMATION (CONTINUED)

DARZALEX® Infusion-Related Reactions

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX® infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX® infusion. If ocular symptoms occur, interrupt DARZALEX® infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX®.

DARZALEX FASPRO® (daratumumab and hyaluronidase-fiIh): Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO®.

Systemic Reactions

In a pooled safety population of 898 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO® as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, Grade 3: 1%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX FASPRO® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO®.
IMPORTANT SAFETY INFORMATION (CONTINUED)

DARZALEX® (daratumumab and hyaluronidase-fihj): Hypersensitivity and Other Administration Reactions

Consider administering corticosteroids and other medications after the administration of DARZALEX® depending on dosing regimen and medical history to minimize the risk of delayed [defined as occurring the day after administration] systemic administration-related reactions. Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliarrhexis, are rare. Ocular complications that require hospitalization have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX® and seek immediate ophthalmologic evaluation prior to restarting DARZALEX®.

Local Reactions

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX®. Monitor for local reactions and consider symptomatic management.

DARZALEX® and DARZALEX®: Neutropenia and Thrombocytopenia

DARZALEX® and DARZALEX® may increase neutropenia and thrombocytopenia induced by background therapy. Monitor complete blood counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX® or DARZALEX® until recovery of neutrophils or for recovery of platelets.

In lower body weight patients receiving DARZALEX® higher rates of Grade 3-4 neutropenia were observed.

DARZALEX® and DARZALEX®: Interference With Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX® and DARZALEX®. Type and screen patients prior to starting DARZALEX® and DARZALEX®.

DARZALEX® and DARZALEX®: Interference With Determination of Complete Response

Daratumumab is a human immunoglobulin G (IgG) kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

DARZALEX® and DARZALEX®: Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX® and DARZALEX® can cause fetal harm when administered to a pregnant woman. DARZALEX® and DARZALEX® may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX® or DARZALEX® and for 3 months after the last dose.

The combination of DARZALEX® or DARZALEX® with lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

DARZALEX®: ADVERSE REACTIONS

The most frequently reported adverse reactions (incidence ≥20%) were upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX® are neutropenia, lymphopenia, thrombocytopenia, leukopenia, and anemia.

DARZALEX® FASPRO®: ADVERSE REACTIONS

In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, headache, pyrexia, cough, muscle spasms, back pain, vomiting, hypertension, upper respiratory tract infection, peripheral sensory neuropathy, constipation, pneumonia, and peripheral edema. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

INDICATIONS

DARZALEX® (daratumumab) is indicated for the treatment of adult patients with multiple myeloma:

- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
- In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
- In combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI)
- As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

DARZALEX® FASPRO® (daratumumab and hyaluronidase-fihj) is indicated for the treatment of adult patients with multiple myeloma:

- In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with carfilzomib and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor (PI)
- In combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
- In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

Please see Brief Summary of full Prescribing Information for DARZALEX® and DARZALEX® FASPRO® on adjacent pages.
**Table 1: Adverse Reactions Reported in ≥10% of Patients and With At Least a 5% Greater Frequency in the DRd Arm in MAIA**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRR (N=364)</th>
<th>DRd (N=350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>57</td>
<td>7</td>
</tr>
<tr>
<td>Constipation</td>
<td>41</td>
<td>1</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>52</td>
<td>2</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>26</td>
<td>14</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>18</td>
<td>2</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection-related reactions</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>61</td>
<td>7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>Asthenia</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Prisoners</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Chills</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>34</td>
<td>4</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Paresthesia</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Hypersensitization</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Hypersensitization</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Dermatologic disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitization</td>
<td>13</td>
<td>6</td>
</tr>
</tbody>
</table>

**Key:** D—daratumumab, Rd—lenalidomide-dexamethasone.

**Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRR (N=364)</th>
<th>DRd (N=350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>90</td>
<td>30</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>81</td>
<td>29</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>84</td>
<td>41</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>67</td>
<td>47</td>
</tr>
</tbody>
</table>

**Key:** D—daratumumab, Rd—lenalidomide-dexamethasone.

**Relapsed/Refractory Multiple Myeloma**

**Combination Treatment with Lenalidomide and Dexamethasone**

The safety of daratumumab in combination with lenalidomide and dexamethasone was evaluated in POLLUX (see Clinical Studies (14.2) in Full Prescribing Information). Adverse reactions described in Table 3 occurred in at least 1% of patients in the DRd arm or meet the threshold for inclusion and were reported in the DRR arm for daratumumab-lenalidomide-dexamethasone (DRd) and of 13.2 months (range: 0.2 to 20.1 months) for the lenalidomide-dexamethasone (LD) arm.

**Serious adverse reactions occurred in 49% of patients in the DRd arm compared with 42% in the Rd arm. Serious adverse reactions included at least 1% more in the DRd arm compared with the Rd arm with at least 1% more in the DRR arm compared with the DRd arm.**

**Adverse reactions in patients with baseline disease characteristics not available for analysis in DRR and DRd include**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRR (N=283)</th>
<th>DRd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>65</td>
<td>6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 3: Adverse Reactions Reported in ≥10% of Patients and Withat Least a 5% Greater Frequency in the D-Rd Arm in POLLUX (continued)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRd (N=283)</th>
<th>Rd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>43</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRd (N=283)</th>
<th>Rd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>95</td>
<td>42</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>Platelet</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Anemia</td>
<td>52</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 5: Clinical Findings in Clinical Trials

<table>
<thead>
<tr>
<th>Body System</th>
<th>DRd (N=283)</th>
<th>Rd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Nervous system</td>
<td>70</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>40</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 6: Drug Interactions

<table>
<thead>
<tr>
<th>Drug Interaction</th>
<th>Details</th>
</tr>
</thead>
</table>
| Daratumumab      | binds to CD38 on RBs and interferes with compatibility testing, including antibody screening and cross matching. |}

Table 7: Pregnancy and Feeding Information

<table>
<thead>
<tr>
<th>Pregnancy and Feeding Information</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy testing</td>
<td>Refer to lenalidomide, pomalidomide, or thalidomide prescribing information for use during pregnancy.</td>
</tr>
</tbody>
</table>
DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

DARZALEX FASPRO® is indicated for the treatment of adult patients with multiple myeloma:
• in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

CONTRAINdications

DARZALEX FASPRO® is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation (see Warnings and Precautions and Adverse Reactions).

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO® (see Adverse Reactions).

Systemic Reactions

In a pooled safety population of 899 patients with multiple myeloma (N=710) or light chain (AL) amyloidosis (N=189) who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 9% of patients experienced a systemic administration-related reaction (Grade 2-3, Grade 3: 1%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred within 6 hours of the start of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions include hypoxia, dyspnea, hypertension, and tachycardia, and ocular adverse reactions, including photophobia, vision disturbance, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids (see Dosage and Administration (2.5) in Full Prescribing Information). Monitor patients for systemic administration-related reactions and, if specifically following the first and second dose, and immediately following the first injection of daratumumab or administration of corticosteroids and other medications after administration of DARZALEX FASPRO depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions (see Dosage and Administration (2.5) in Full Prescribing Information).

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt daratumumab-containing products and seek immediate ophthalmologic evaluation prior to restarting DARZALEX FASPRO.

Local Reactions

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO. Monitor for local reactions and consider symptomatic management.

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone (see Warnings and Precautions). Serious cardiac disorders occurred in 16% and fatal cardiac disorders occurred in 6% of patients. Patients with NYHA Class III or Mayo Stage III disease may be at greater risk. Patients with NYHA Class IIIB or IV disease were not studied.

Monitor patients with cardiac involvement of light chain (AL) amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate.

Neutropenia

Daratumumab may increase neutropenia induced by background therapy (see Adverse Reactions). Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Continuously withhold DARZALEX FASPRO until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia

Daratumumab may increase thrombocytopenia induced by background therapy (see Adverse Reactions). Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX FASPRO until recovery of platelets.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 6 months after the last dose (see Use in Specific Populations).

The combination of DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide or pomalidomide may cause birth defects and other adverse outcomes. In the female fetus, lenalidomide and dexamethasone may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to avoid becoming pregnant during treatment with DARZALEX FASPRO and for 6 months after the last dose (see Use in Specific Populations).

Dosage interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient were pneumonia and anemia.

The most common adverse reactions (≥20%) were fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO in PLEIADES.

Table 1: Adverse Reactions (≥20%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue¹</td>
<td>54</td>
<td>9</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection²</td>
<td>44</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonia³</td>
<td>23</td>
<td>17</td>
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<tr>
<td>Bronchitis²</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Back pain</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
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<tr>
<td>Dyspnea</td>
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<tr>
<td>Cough¹</td>
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<td>Psychiatric disorders</td>
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<tr>
<td>Insomnia</td>
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</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

¹ Fatigue includes asthenia, and fatigue.
² Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
³ Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.

Table 2: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>94</td>
<td>34</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82</td>
<td>56</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>49</td>
<td>3</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>89</td>
<td>52</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45</td>
<td>8</td>
</tr>
</tbody>
</table>

¹ Denominator is based on the safety population treated with DARZALEX FASPRO-Rd (N=65).
DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

Immunogenicity
As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is less a measure of sensitivity and specificity of the assay, than a measure of any intrinsic ability to generate antibodies against daratumumab. The incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other daratumumab products or other hyaluronidase products may be misleading.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, less than 1% of 819 patients developed treatment-emergent anti-daratumumab antibodies.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 3% of 812 patients developed treatment-emergent anti-hyaluronidase antibodies.

In patients with APO-FASPRO, the anti-hyaluronidase antibodies did not appear to affect daratumumab exposure. None of the patients who tested positive for anti-hyaluronidase antibodies tested positive for neutralizing antibodies.

Postmarketing Experience
The following adverse reactions have been identified with post-approval use of daratumumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immunologic: Anaphylactic reaction, Systemic administration reactions (including death)
Gastrointestinal: Pancreatitis
Infectious: Cytomegalovirus, Listeriosis

DRUG INTERACTIONS
Effects of Daratumumab on Laboratory Tests
Interference with Indirect Antiglobulin Tests (Indirect Complement Tests)
Daratumumab binds to CD38 on red blood cells (RBCs) and interferes with complement testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding [see References] or genotyping. Since the Kel blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched AB0/Rh0-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests
Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In DARZALEX FASPRO-treated patients with AL amyloidosis, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS
Preparation
Risk Summary
DARZALEX FASPRO® can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and the known potential of CD38 knockout animal models [see Data]. There are no available data on the use of DARZALEX FASPRO in pregnant women to evaluate drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

The combination of DARZALEX FASPRO® and lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women because of the known potential of CD38 knockout animal models and the known risk of fetal loss and death of the unborn child. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

Clinical Considerations
Fetal/Neonatal Adverse Reactions
Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Delegate administering live vaccines to neonates and infants exposed to daratumumab in utero until a hematology evaluation is completed.

Data
Animal Data
DARZALEX FASPRO® for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal bone marrow transplantation and immunoglobulin G1 (IgG1) monoclonal antibodies that cross the placenta. Based on its known potential of CD38 knockout animal models and the known risk of fetal loss and death of the unborn child. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

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Oncology Care Model (OCM), which ran from 2016 until June 2022, seemed to be a good fit for Compass initially. The practice was already delivering palliative care, and leaders believed the practice’s metrics would compare favorably to area competitors.

But early on, Compass was disappointed. Cosgrove said. It was hard to achieve savings until the practice had a “laser focus” on managing the cost savings and quality-of-life metrics. “With biosimilars, we saw cost savings at the end of the program,” he said.

Maintaining that focus was difficult during the COVID-19 pandemic, when practices had to deal with implementing telehealth and staffing shortages. Some models start with high ideals, Cosgrove said, but for those working them day to day, “there’s the perception, ‘I have to do my work and then this?’”

Kruger, whose practice serves some of the poorest areas in Virginia and North Carolina, had a more positive view of value-based care. “We’re a better practice because of it,” he said. Personnel shifts have directed more resources into patient services, including helping patients identify community resources for food or programs that can support drug costs.

The process of working with other agencies has allowed the practice to build partnerships and trust that go beyond delivering care. “It’s improved quality and changed our standing in the community,” he said.

OneOncology practices have worked with multiple payer models beyond the OCM. Lyss said, including oncology models developed by Aetna, Cigna, and Humana; Astera Cancer Care, which is among the 15 OneOncology practices, has worked on value-based models with Horizon BlueCross BlueShield of New Jersey. Although that experience is valuable, Lyss said the variation between different oncology models can create management challenges for a practice.

When there are different quality or clinical data reporting requirements across models, he said, “even if 80% are the same, that 20% difference is really difficult to manage,” both at the point of care and at the administrative level.

Lyss highlighted the need for regular, ongoing contact. OneOncology’s formation, which Lyss said results in the culture change that is critical for success when operating value-based payment models. “That doesn’t happen overnight,” he said.

Diaz asked the panelists to elaborate on current challenges with “carve-outs,” which are exceptions to overall value-based contracts among commercial payers that require practices to deviate from standard procedures. These requirements have increased as payers have become vertically integrated with pharmacy benefit managers and other health care delivery entities. As Lyss explained, carve-outs typically mean money for the payer and headaches for the practice.

“The payer will use their preferred vendor or vertical integrated joint venture for services that the practice wants to provide for the patients—especially services that are key to driving performance,” Lyss said. When there’s no transparency—especially in areas such as specialty pharmacy or imaging services—it makes it hard for practices to manage costs and quality.

OneOncology practices have worked with multiple payer models beyond the Oncology Care Model, including models developed by Aetna, Cigna, and Humana; Astera Cancer Care, which is among the 15 OneOncology practices, has worked on value-based models with Horizon BlueCross BlueShield of New Jersey.

“We’ve been successful in making the case why the OneOncology practices should be empowered in these models to manage patient care in these services,” he said.

Said Diaz, “We can see that in my practice, too. And the way I like to summarize it is that when patient care is fragmented, it makes it very difficult for the person who’s supposed to be quarterback in all of this…. Because these other parties aren’t necessarily aligned.”

Kruger said he’s seen this in his area, where hospitals refuse to use less expensive biosimilars because they’d rather get the financial windfall from branded medications under the 340B program. “They want people to go to infusion centers,” Kruger said. “I don’t think they do as well as they think they do, and they charge 5 times as much for the drug.”

Diaz asked how practices that have worked with value-based payment models with one population—most likely Medicare patients—can start conversations to expand to other patient groups.

Kruger said this can be challenging if data are not available. An effort in his area to bring more alignment among psychological services has stalled for this reason. “As difficult as the lack of data is for us, the hospital also has a lack of data,” he said.

Encouraging “smaller bites of the apple” is a good place to start, Kruger said. “I can control where the patient goes, and how many times I see them,” he said. If needed, patients can come in more often. Kruger can decide when to start palliative care. When it comes to community services such as transportation or help with groceries, he said, “Sometimes you just have to ask, and you’ll be surprised what you’ll get.”

Lyss highlighted the need for regular, ongoing contact. OneOncology’s practice, Tennessee Oncology, works closely with BlueCross BlueShield of Tennessee and is in contact weekly on how to address issues such as steerage or reduction in utilization.

In response to a question, Lyss said the experiences of the past decade in value-based care—including the years in the OCM—are what a management
services organization such as OneOncology offers practices that have not tried value-based care but are considering the Enhancing Oncology Model (EOM).

Lyss acknowledged that parts of the journey were “painful” for the practices that were early adopters. “It took a long time to get the practice redesign that those practices have now,” he said. He warned that practices that are still holding out must understand that staying with the Merit-based Incentive Payment System (MIPS) will not be easy, because MIPS will change, too. A “critical ingredient” is appreciating the need for culture change. “If a practice is willing to do that—if they’re bought in on the culture change front—there are a lot of other problems that will really help them solve…. And once we have those, we [will] be able to help our clients to succeed in the EOM.”

EOM Creates a Heavy Lift for Small Practices, Leading Oncologists Say

LEADING ONCOLOGISTS SAID that the proposed Enhancing Oncology Model (EOM), which would take effect next July, requires practices to take on more risk and data collection with less guaranteed revenue, making it too much to ask for many small practices—especially those without experience in value-based care.

Michael Diaz, MD, president and managing physician, Florida Cancer Specialists & Research Institute, moderated the panel, “Practice Perspectives on the EOM: Why or Why Not Participate?” featuring:

• Sibel Blau, MD, president and CEO for the Quality Cancer Care Alliance (QCCA), and medical director, Oncology Division, Northwest Medical Specialties, PLLC;
• Susan Escudier, MD, FACP, vice president, Value-Based Care & Quality Programs, Texas Oncology; and
• Barbara McAneny, MD, FASCO, MACP, CEO of New Mexico Cancer Center, Ltd, and past president, American Medical Association.

The Center for Medicare and Medicaid Innovation (CMMI) unveiled the EOM in late June as the successor to the Oncology Care Model (OCM), which had drawn on the experience of McAneny’s COME HOME project in creating a model designed to improve outcomes and patient experience while reducing cancer care costs.

The EOM clearly draws on lessons from the OCM experience but with some key differences:

• All practices must take on risk right away, regardless of size or experience with value-based care.
• The EOM has 2 risk tiers: The lower-risk tier will not let a practice escape reporting under the Merit-based Incentive Payment System (MIPS). Practices that followed the OCM did not have to report under MIPS.
• The EOM will impose additional data reporting requirements on social determinants of health (SDOH) while at the same time cutting monthly payments to deliver added services.
• The EOM will focus on 7 types of cancer, so fewer patients will be covered under the model—which means less revenue to run patient navigation and other services.

Blau said 11 of the 18 QCCA practices have applied for the EOM, and some elements show that CMMI listened to feedback from oncologists based on the OCM. Her initial reaction to the EOM was, “It’s good that it’s here,” but whether the numbers will work for the smallest practices is an open question.

With the OCM, she said, practices had time to learn the model before taking on risk. “I can’t imagine a non-OCM practice taking on this with no history and experience.” Blau said, especially with EOM changes that restrict the number of covered patients to 7 disease types. The smaller number of patients will make it very difficult to earn a pay-for-performance bonus, and the additional requirements for inclusion of electronic patient-reported outcomes (ePROs) will be challenging for some.

“Our practice was pretty successful with the OCM,” Escudier said. “I think it instituted some favorable changes in practice in terms of some of the patient-centric features; the care plans, I liked a lot.”

As for the EOM, her first reaction was, “Gosh, they’re asking us to do more for less.”

Escudier noted, as others have, that with the EOM covering only a portion of the Medicare population, practices will face a choice of what to do about offering added services, such as navigation or 24/7 access to medical records, to all patients. The consensus is that practices will treat all patients the same way.

She also questioned whether oncology practices had the capacity to solve problems of poverty, transportation, and other social conditions alongside treating patients’ cancer.

Diaz and McAneny said they have observed many of the same issues. “In the EOM, the chances of rewards are not that big, but the chances of loss are big,” McAneny said, and this could crush smaller practices that have large numbers of patients in rural areas. The risk scenarios presented in the EOM could put some small practices out of business, she said, and what happens to the patients? If the doctors are absorbed by a hospital system, costs for Medicare will increase.

“We don’t mind being held accountable,” Diaz said. “But we aren’t necessarily graced with having these large potential positive upsides…. Because when we’re talking about risk, it’s not just for the cost of their cancer care.”

McAneny also took issue with the SDOH data collection, which she said would create cultural issues with the Native American populations she serves. Approximately 48% of McAneny’s patients are Medicaid eligible and 12% receive coverage from the Indian Health Service.

“First, it’s very important in terms of looking at this from the viewpoint of the people we’re trying to impact,” she said. Data collection “is a very dominant culture” to a group that doesn’t see this as a way to solve problems, she said, “so, we’re starting with that bias.”

“Secondly, when you collect data, you are implying to people that you’re actually going to do something better. And, as [Escudier] just said, oncology practices are not going to fix poverty or racism, which are the key issues of the [SDOH]. We don’t have the bandwidth to do that.”

“Third, I really have some concerns about collecting these data and sending [them] to the federal government.” The Navajo Nation population she has served for 15 years has deep mistrust of the federal government. Over a 400-year period, McAneny said, every time the government collects data, “they get moved to less desirable territories, the benefits get taken away, and treaties get broken.

“It’s not easy for somebody who looks like me to establish some street cred with people who live in that population…. Am I willing to put that acceptance that is hard fought on the line to collect data to give to the federal government, when nothing is going to come back to that population that will be of value to them? That is really something that I’m struggling with.”

Blau offered some warnings for ePROs, which she said can be important for managing symptoms but have to be deployed with extreme care. “If a practice is not savvy, patients will be complaining about everything,” and this could overwhelm a small practice.

Escudier said her practice had developed a system for managing patient symptoms and needed to maintain control over it. McAneny agreed, saying that giving patients unrestricted ability to call in symptoms could have unintended consequences. “Patient satisfaction can drop from this instead of increase,” which in turn could drive more clinicians out of practice.

“It’s not ideal to have a one-size-fits-all solution,” Diaz said. •
ONEONCOLOGY PHYSICIAN LEADERSHIP CONFERENCE

Exploring the Quest for the “Secret Sauce” in Oncology on an Unequal Playing Field

JEFF PATTON, MD, the CEO of the practice network OneOncology, said he had given up the hope of ever seeing reform of 340B, the government program that lets safety-net hospitals buy prescription drugs at discount and then bill insurers the full price, creating a profit stream unavailable to community oncologists.

But in September, The New York Times reported on the case of Bon Secours in Virginia, Patton's home state. The Richmond-based health care giant had taken advantage of Richmond Community Hospital to quality for 340B, then stripped out the hospital's specialists and equipment until it was a "glorified emergency room," with no intensive care unit to care for patients with COVID-19. Meanwhile, Bon Secours' suburban facilities boomed—all billing off the lucrative drug program.1

For Patton, the report was a sign that complaints about 340B from the Community Oncology Alliance are finally breaking through. "I've gone from hopeless to having some hope," he said.

Patton related the Bon Secours episode November 11 as he opened the OneOncology Physician Leadership Conference, a 3-day gathering in Nashville, Tennessee, of providers from the 15 practices that make up the growing network, which offers data analytics, clinical pathways, marketing, and administrative support to help community oncology compete in what Patton described as an uneven playing field.

"If health care were a free market, we would have already won," he said, describing community oncology as the "low-cost, high-quality provider in cancer care." Powerful forces work in favor of hospitals, from their status as a major employer in rural areas to their lobbying clout. Patton explained that these advantages work against community oncology in many ways:

- When health systems buy up primary care physician practices, those patient referrals no longer flow to community oncology.
- Laws requiring price transparency, which should let low-cost providers compete, are hampered by “anti-steerage clauses” that hospitals put in payer contracts.
- Vertical integration, which has gained attention from the Federal Trade Commission, is allowing insurers to make more money from their associated pharmacy benefit manager (PBM). Practices are blocked from using lower-cost drugs or biosimilars due to rebate arrangements.
- Because of 340B, hospitals are financially rewarded for avoiding low-cost options, including biosimilars.

Meanwhile, Patton said, the headwinds continue for community oncology, which must absorb 7% inflation and a 4.5% pay cut under the most recent Physician Fee Schedule.2

OneOncology, he said, is helping practices push back against all these trends. "In the past 2 years, we've doubled in size—our physician practice number, revenue, and earnings have gone up 50% year over year, despite the ugly forces out there," Patton said.

A key to OneOncology's success, he said, is helping practices grow within their markets and gain bargaining power with area payers. (Two OneOncology practices, Tennessee Oncology and Astera Cancer Care in New Jersey, have executed innovative value-based agreements with their respective Blue Cross Blue Shield insurers.) "If you can get dominant or close-to-dominant market share in your local practice [area], you can win," Patton said.

OneOncology aids practices with physician recruiting, at a time when more medical oncologists are retiring than being trained. Patton highlighted rapid growth at Fort Worth, Texas-based The Center for Cancer and Blood Disorders and on Long Island, with New York Cancer and Blood Specialists.

He said the OneOncology philosophy rests on several core principles: a passion for clinical research, a commitment to value-based care, a data-driven approach that uses measures to drive improvement, and a belief that all discussions start with what makes sense from a clinical perspective.

"We're doctors and care providers first," Patton said, highlighting OneCouncil, a physician-led board that drives issues affecting clinical practice.

"We have an incredible value proposition to tell," he said. Community oncology is decreasing hospitalization and driving down costs—just taking a patient from a hospital to a community clinic cuts infusion costs by two-thirds. Today, the challenge is helping practices meet compliance requirements while maintaining "that Mom-and-Pop feel" that patients prefer and delivering the most innovative treatments.

"That's our secret sauce," Patton said.

LESSONS FROM GOVERNMENT SERVICE. Patton welcomed Adam Boehler, the current CEO of Rubicon Founders; Boehler served in the Trump administration as head of the Center for Medicare and Medicaid Innovation (CMMI). Boehler, who previously founded the home health company Landmark Health, had never pictured himself in government. He was recruited by officials who left CMS after the end of the Obama administration for his ability to “align incentives.” On his watch, CMMI made important adjustments to the Oncology Care Model (OCM) and developed kidney care models.

"If health care were a free market, we would have already won," said Jeff Patton, CEO of OneOncology, describing community oncology as the “low-cost, high-quality provider in cancer care.”

Patton and Boehler discussed challenges with health care generally and the those that community oncologists face specifically. Boehler described the challenge of creating positive incentives, and then Patton asked about the transition to the Enhancing Oncology Model (EOM), proposed in July as a slimmed-down successor to the OCM. Specifically, Patton asked about the reasons for a yearlong gap between the 2 models; this, he predicted, will cause quality reporting headaches for practices that may want to move from the OCM to the EOM. Is it just politics?

More likely, Boehler said, the yearlong gap is due to the transition between administrations—top staff in the White House are focused on issues such as the war in Ukraine, not CMMI. Beyond that, models are not designed to be permanent fixtures. "If you rely too much on them...if all your economics were based on that, that's a bad idea, it's risky," Boehler stated.

Building around bundled payments makes sense in certain cases, but not in others, he said. In trying to solve problems, it can often make sense to invest in a partner with aligned goals—Patton mentioned full-risk primary care. Boehler said that primary care groups would be most interested in nephrology and oncology; when he was with Landmark, he noted, “we would always be interested in working with oncologists, because we know where to stop.”
Providers Must Educate Congress, CMS on Reality of Oncology Practice Finances, Patel Says

AS CMS MOVES TO IMPLEMENT the Inflation Reduction Act (IRA) as well as the Enhancing Oncology Model (EOM), leading oncology providers must educate both Biden administration officials and members of Congress on how the new law and ongoing efforts addressing payment reform could impact community oncology. Kavita Patel, MD, MS, discussed strategies at the first OneOncology Physician Leadership Conference, held November 11 to 13 in Nashville, Tennessee.

Patel, a primary care physician and former Obama administration policy official, is now a senior policy adviser at Stanford University and a venture partner with New Enterprise Associates. She is also a member of the editorial board at The American Journal of Managed Care®. In Nashville, Patel offered a wide-ranging talk that covered policy issues affecting community oncology. Patel said that although she was “not a fan” of the EOM, which the Center for Medicare and Medicaid Innovation will launch on July 1, 2023, to replace the Oncology Care Model (OCM), “it’s not going away.”

The EOM has been praised by some for retaining and promoting the best features of the OCM, such as patient navigation and same-day appointments to reduce hospital stays. But detractors say it allows no time for smaller practices to ease into value-based care before they face punitive financial models that could shutter a practice over a misstep.

Patel explained that the movement to models that are more heavily focused on downside risk continues a trend that started in the Trump administration—and one that has little to do with politics. The “carrot-and-stick” approach to downside risk can present challenges for oncology practices, which Patel noted offer complex care and need capital to pursue innovation.

INFLATION REDUCTION ACT. Describing the IRA as the most significant change to health care since the Affordable Care Act, Patel offered details on the impact and implementation of the new law, which will be phased in over 6 years from 2023 to 2029. Chief elements include a $2000 annual out-of-pocket cap for Medicare Part D, starting in 2025, and price negotiations for 10 high-cost drugs in Medicare Parts B and D starting in 2026, moving to 20 drugs by 2029.1

“Notice that it’s very clear that physicians or providers are not on here,” she said, reviewing a complex slide outlining the implementation schedule.

In recent years, leaders of OneOncology and other members of the Community Oncology Alliance have raised alarms about the problem of direct and indirect renumeration (DIR) fees, which are caused by a Medicare loophole that allows pharmacy benefit managers (PBMs) to charge pharmacy fees tied to quality measures. For oncologists who manage an in-house pharmacy, these DIR fees are exasperating, because they can show up months or even a year after a drug is prescribed and be tied to measures well beyond the scope of cancer care.

Patel warned that policy makers and members of Congress need more education on the realities of community oncology practice finances, including intricacies like DIR fees. The drugs covered under IRA price negotiations will, by definition, be high-cost drugs, and there could be fallout for practices. “Are you going to get stuck with DIR [fees] coming out?” Patel asked.

Aspects of the IRA seek to shield smaller biotechs from the law’s impact, and Patel warned that pharmaceutical companies, health plans, and PBMs are hard at work looking for ways to protect themselves from losing money. With the downward pressure on out-of-pocket costs for consumers, however, “there is opportunity for actually something good to come out of it,” she said. “If there’s more affordable drug coverage, then there could be a boost in enrollment.”

Some models show that Medicare Part D enrollment could rise from 74% of beneficiaries to 85% or 95%, she said.

Implementation of the law will be key, and CMS is building an office with personnel who have drug pricing expertise. Patel also noted that models from the Congressional Budget Office don’t factor in how the commercial sector will respond to Medicare decisions under the IRA, but oncology practices won’t have a choice. “There are still a lot of questions about what segment of the population this [law] hits, and how this will affect them,” she said.

Patel warned oncologists to demand a seat at the table, so that policy makers gain an understanding of the business side of oncology. “All of this will happen in a very murky, poorly constructed manner, unless you give inputs and try to say, ‘Let me explain to you what happens when I have a cancer patient who’s on this particular drug that we have that thrive. And here’s why we do this. And here’s what [a] DIR [fee] does. Here’s exactly what the finances are,’” she advised. “That level of understanding never comes into play.”

 Herbalife Nutrition with Newsmakers

PATEL

Changing Culture and Finding Champions: Licitra, Arrowsmith Discuss Value-Based Care in Oncology

IMPLEMENTING VALUE-BASED CARE in an oncology practice is a journey, one that demands commitment from every member of the organization and a culture shift that takes time, according to 2 practice leaders taking part in the OneOncology Physician Leadership Conference in Nashville, Tennessee. Edward Licitra, MD, PhD, who is CEO of Astera Cancer Care, based in East Brunswick, New Jersey, and Edward “Ted” Arrowsmith, MD, of the Chattanooga office of Tennessee Oncology, shared ideas during a panel discussion at the OneOncology Physician Leadership Conference, held November 11 to 13 in Nashville, Tennessee. Sheri Chatterton, MSM, MBA, CFHP, vice president of payer relations for OneOncology, led the discussion.

Chatterton started by asking how practices arrived at value-based contracts, which are needed to implement value-based care. Both Tennessee Oncology… »
and Astera have reached value-based contracts with the Blue Cross Blue Shield (BCBS) entities in their respective states.

“When we do the right thing, we’re always focused on doing the right thing for the patient. The rest of it will follow along,” Licitra said. “We’ll get alignment of incentives, we’ll get better outcomes, we’ll build a better model.”

He acknowledged that value-based care can mean different things to different people. On one end of the continuum are those who start by setting up an oncology medical home, offering Humana’s model as an example. “That’s really the foundation,” Licitra said. “If you don’t build a strong foundation, and if you don’t build a comprehensive value-based care home that evolves over time and gets better based upon all the experiences that happen…you really don’t have much.”

On the other end of the continuum, value-based care moves toward capitalization, which could be “transformational,” said Licitra, but extreme care is required. Shared savings models, including the Oncology Care Model (OCM), are retrospective in nature; the OCM started as a 1-sided risk model to train practices and evolved into a 2-sided risk model.

“Unless you have a willing partner who is ready to sit down, roll up [their] sleeves, and actually work together toward a common objective, none of these things ever work.”

—Edward J. Licitra, MD, PhD, CEO, Astera Cancer Care

Arrowsmith said that value-based models have evolved because cancer care has become expensive, “and there’s not that enthusiasm for just writing a blank check to pay for whatever it is that you do.” Payers, he said, want to see constructs such as pathways to bring more standardization to care, to drive down costs, and to prevent unnecessary emergency department (ED) visits and hospitalizations. Tennessee Oncology was able to reach a contract with BCBS of Tennessee, the state’s largest payer, which is “toward the beginning of the continuum,” and requires certification of lessons learned over 5 years and proof of quality care.

From there, Arrowsmith said, Tennessee Oncology was able to “get into the room” with BCBS to negotiate a contract that spells out what the practice can and cannot control, specific targets, and margins to beat.

Chatterston asked Licitra and Arrowsmith about the nature of relationships with vendors under value-based care.

Licitra emphasized the need for partnerships. “Unless you have a willing partner who is ready to sit down, roll up [their] sleeves, and actually work together toward a common objective, none of these things ever work,” he said. In New Jersey, Astera was fortunate to have a willing partner in Horizon BCBS, and the 2 entities started 4 years ago working together on cancer episodes. “We started out with medical oncology, then added radiation oncology and breast surgery,” Licitra said.

The episodes had to be well defined, by certain lengths of time, and Astera had to be able to construct the episode for each patient who “didn’t have to pay attention to fee-for-service.”

Licitra said that payers like this approach because it offers a deeply discounted rate compared with similarly bundled services. “It actually reduces a lot of the burden on both the patient and the physician, because they’re not worrying about getting things approved,” he noted.

Arrowsmith added that value-based contracts can be customized to highlight a practice’s strengths and minimize its weaknesses. Whereas Astera has a breast cancer model that includes its breast cancer surgeons and radiation centers—and can include lower charges for those services than the payer would see from a hospital—Tennessee Oncology leaves those items out.

Next, Chatterston asked what it takes to change a practice’s culture.

“Culture isn’t one big thing you do,” Arrowsmith said. “It’s a thousand little things you change over time.” Doctors and nurses want to do the right thing—it’s about thinking of ways to incentivize all the little things that improve care and patient experience.

It’s not simple, Licitra said. “If it was just a handful of things, everyone would do it,” he pointed out.

The shift in mindset, Licitra pointed out, goes beyond optimizing clinical variables to a change in approach, which means much more than doing something inappropriate. “Once you enter value-based care arrangements, the physicians have to think about the world of medicine very, very differently,” he said.

And it’s not just the physicians: The triage nurses, the chemotherapy nurses, and the rest of the staff all must think through the consequences of what their decisions might mean that day, as well as several days or months ahead. “It takes a lot of work to make sure that you continuously provide physicians with data,” said Licitra. “You have to provide them with reliable data, because they all say that your data are wrong. Provide us with reliable data and make sure that before you go into the meeting, that your data are actually correct.”

So, where does a practice begin if members want to venture into value-based care?

“Find a champion—or a few champions—for value-based care,” Licitra replied. Without that lead physician, administrator, or pharmacist who is passionate about making the culture change and the execution work—about doing the right thing—it will be hard to evolve.

“You think about it as kind of a challenge, because a lot of work has to actually happen to be successful,” continued Licitra. “Without the proper leadership and the proper champions for it, I think it’s tough to do.”

Arrowsmith suggested identifying the key levers, such as keeping patients out of the ED, which can make a significant difference. And, he said, “Don’t give up.”

Some ideas that practice members might think are terrific might fall flat with payers, Arrowsmith said, but it’s important to keep talking. It took Tennessee Oncology 5 years to reach their agreement with BCBS of Tennessee.

The physicians said that starting with a framework the payers are already using and adapting an idea to fit that model works much better than presenting something completely different. And once a practice has implemented the first model, Licitra said, “the rest are a lot easier.”

CONTINUED ON SP558
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ILCA 2022

Pemigatinib Improves OS in FGFR2-Altered Cholangiocarcinoma

Jonah Feldman

PEMIGATINIB (PEMAZYRE®) showed a strong survival benefit in patients with previously treated advanced cholangiocarcinoma who had an FGFR2 fusion or rearrangement, according to final results of a study presented at the International Liver Cancer Association (ILCA) Annual Conference 2022.1

In the single-arm phase 2 FIGHT-202 trial (NCT02924376), pemigatinib was associated with a median overall survival (OS) of 17.5 months (95% CI, 14.4-22.9) for patients with cholangiocarcinoma and FGFR2 mutations at a median follow-up of 42.9 months (range, 19.9-52.2), whereas patients without these genetic alterations had shorter OS and progression-free survival (PFS).

"The OS remains one of the highest in regard to cholangiocarcinoma at 17.5 months," Ghassan K. Abou-Alfa, MD, said during his presentation at ILCA.

Pemigatinib is an oral, selective FGFR1, FGFR2, and FGFR3 inhibitor that has been investigated for use in patients with cholangiocarcinoma, an epithelial tumor of the bile duct. The primary results of this trial led to pemigatinib’s FDA approval for patients with previously treated unresectable, locally advanced, or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement.2

Patients were enrolled in FIGHT-202 if they had documented FGF/FGFR status and progression after at least 1 prior therapy for cholangiocarcinoma. There were 3 distinct cohorts. Cohort A consisted of 108 patients with FGFR2 fusions or rearrangements; cohort B consisted of 20 patients with other FGF/FGFR genetic alterations; and cohort C consisted of 17 patients with no FGF/FGFR genetic alterations. Patients were required to have adequate liver and kidney function and Eastern Cooperative Oncology Group performance status of 2 or better.

The primary end point was objective response rate (ORR) by independent central review in cohort A. Secondary end points included ORR in cohorts A and B combined; ORR in cohorts B and C individually; and duration of response (DOR), disease control rate (DCR), PFS, OS, and safety for all cohorts. Patients received 13.5 mg of pemigatinib orally each day for 2 weeks followed by 1 week with no therapy, which was repeated until progression, death, or unacceptable toxicity.

The baseline characteristics of patients in the trial showed some differences among the cohorts. Cohort A included a greater proportion of women (61%) and younger patients (median age, 55.5 years [range, 26-77]) than other cohorts, and the longest time from initial diagnosis with cholangiocarcinoma (median, 1.3 years [range, 0.2-11.1]).

“We noticed that the 1.3 years until patients start on therapy for the FGFR2 alteration might reflect that this population has certain advantages with the alterations to begin with, which is of course benefiting from the pemigatinib in that setting,” said Abou-Alfa, an attending physician at Memorial Sloan Kettering Cancer Center in New York, New York. In addition, 99% of patients in cohort A had intrahepatic cholangiocarcinoma vs 65% and 59% in cohorts B and C, respectively.

A lower percentage (82%) in cohort A had metastatic disease vs 100% in cohort B and 94% in cohort C.

Among the total population, 39% had received 2 or more prior lines of therapy. At a median follow-up of 42.9 months (range, 19.9-52.2), the ORR for cohort A was 37% (95% CI, 28%-47%). At a median follow-up of 47.5 months (range, 43.7-51.1), ORR was 0% (95% CI, 0%-17%) for cohort B. At a median follow-up of 51.9 months (range, 49.5-53.7), ORR was 0% (95% CI, 0%-20%) for cohort C. The DCR was 82% for cohort A, 40% for cohort B, and 18% for cohort C. Cohort A included 3 complete responses.

Among 104 evaluable patients in cohort A, the median best percentage change in the sum of the target lesion diameters from baseline was –28.4% (range, –100% to 55%). The median DOR for cohort A was 9.1 months (95% CI, 6.0-14.5). The median PFS for this cohort at final analysis was 7.0 months (95% CI, 6.1-10.5). For cohort B, median PFS was 2.1 months (95% CI, 1.2-4.9). For cohort C, median PFS was 1.5 months (95% CI, 1.4-1.8). In contrast to the median OS of 17.5 months observed for cohort A, cohort B had a median OS of 6.7 months (95% CI, 2.1-10.6) and cohort C had a median OS of 4.0 months (95% CI, 2.0-4.6).

In regard to cohorts B and C, you can see that they were not up to the same par as cohort A, understandably because of the criticality of the FGFR2 fusion, even though the patients at least with FGFR genetic alterations of other kinds had some benefit,” said Abou-Alfa, noting the moderate PFS and OS improvement in cohort B vs cohort C, although the cohorts were not directly compared.

Safety was consistent with the primary analysis and no new safety signals were reported. The most common any-grade treatment-emergent adverse event (TEAE) was hyperphosphatemia at 59% among all patients, but none of these instances were grade 3 or higher. Grade 3 or higher TEAEs were reported in 69% of patients. The most common grade 3 or higher TEAE was hypophosphatemia, at 14.3%. Other common lower-grade TEAEs included alopecia (50%), diarrhea (48%), fatigue (44%), and nausea (41%). The rate of treatment discontinuation due to a TEAE was 10.2%.

“The safety profile continued to be manageable and the fears that we had especially in regard to hypophosphatemia are not necessarily evident, and at the same time, specifically for pemigatinib, we don’t see that much of the skin toxicity either,” Abou-Alfa said.

Overall, these results support the use of pemigatinib in the previously treated FGFR2-altered population and emphasize the role of biomarker testing to identify these patients with cholangiocarcinoma. “The results emphasize 2 important things...it’s very important and urgent to make sure that we get the genetic testing for all the patients as early as possible, and at the same time make sure that this therapy is available for them in the second line, [or after] the second-line setting as well,” Abou-Alfa concluded.

This article first appeared in Targeted Oncology®.

REFERENCES
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Administration for Pegfilgrastim Biosimilars Should Minimize Clinic Visits, Consider Patients’ Preferences

Deana Ferreri, PhD

AUTHORS OF A REVIEW ARTICLE examined administration options and economic considerations for pegfilgrastim biosimilars in supportive oncology in the United States with the aim of maximizing the benefit to patients. Because of the “growing acceptance of same-day pegfilgrastim administration and the ever-present financial burden of medications for patients,” the authors said, these are pertinent topics. Their review discussed administration options with a focus on minimizing clinic visits and proposed a patient-centric model of pegfilgrastim administration for febrile neutropenia prophylaxis.

The granulocyte colony-stimulating factor (G-CSF) biologics filgrastim and pegfilgrastim are used to reduce the risk of febrile neutropenia in patients undergoing myelosuppressive chemotherapy, by stimulating production, maturation, and survival of neutrophils. According to the authors, febrile neutropenia can delay treatment and necessitate dose reductions, limiting the efficacy of treatments and negatively affecting patient health or reducing survival rates. Of the 2, pegfilgrastim, which is a pegylated, long-acting form of filgrastim, is the most commonly used G-CSF in the United States.

Although the high cost of biologics can limit access to treatments, the authors noted that lower-cost pegfilgrastim biosimilars have been available for several years. There are currently 6 pegfilgrastim biosimilars approved in the US for prophylaxis of febrile neutropenia. The reviewers wrote that cost savings could have a “significant impact on the financial stress experienced by patients with cancer,” citing research that found up to 48% of cancer survivors experience financial toxicity. They added that financial stress can cause survivors to skip future medical treatments.

Administration Options for Minimizing Clinic Visits

In general, pegfilgrastim is administered once per chemotherapy cycle and is usually injected 24 hours or more after chemotherapy. Although the FDA-approved indication for febrile neutropenia prophylaxis is next-day administration at the clinic, the authors said multiple options are available. For example, The National Comprehensive Cancer Network also supports same-day administration, which they said has been helpful for minimizing clinic visits during the COVID-19 pandemic. The authors added that same-day administration is likely preferable for patients who live far from the clinic or prefer to minimize visits because of “emotional and physical exhaustion following chemotherapy.”

The reviewers discuss the positives and negatives associated with the 3 approaches to pegfilgrastim administration that minimize clinic visits:

- Same-day administration after chemotherapy
- Use of an on-body injector (OBI) that delivers pegfilgrastim approximately 27 hours after chemotherapy
- Self-administration by the patient or a caregiver at least 24 hours after chemotherapy.

Their view is that “consideration of each option should be based on the individual patient-specific needs and comfort level.” Although self-administration reduces clinic visits and may improve quality of life for patients, correct self-injection techniques are crucial. Barriers to self-injection include fear, anticipated pain, patient age, and comorbidities. The OBI device is applied the same day as chemotherapy and delivers a standard dose of pegfilgrastim 27 hours after application. Failure rates for the OBI range from 1.7% to 6.9%. Not all patients accept the device, and “patient education may be required to ensure the effectiveness of pegfilgrastim OBI and to handle device failure.”

The OBI provides an alternative to self-injection, but OBI devices that deliver biosimilar pegfilgrastim at a lower cost are currently unavailable. According to the authors, 1 pegfilgrastim biosimilar (pegfilgrastim-cbqv) OBI is in development.

The third option for minimizing clinic visits is the off-label use of same-day injection of pegfilgrastim following chemotherapy. This option still eliminates the second clinic visit, and it may be a preferable option for patients who are unable or unwilling to self-inject pegfilgrastim and are uncomfortable having the OBI device attached to their skin. According to the reviewers, concerns about same-day administration originated from observations that shorter-acting filgrastim could exacerbate neutropenia in some cases. “However, same-day administration of pegfilgrastim is not uncommon in clinical practice, and an increasing number of studies across various tumor types have not detected differences in outcomes compared with next-day administration,” they wrote.

Same-Day Pegfilgrastim Administration in the Context of COVID-19

The reviewers said that minimizing clinic visits is an important objective, since patients with cancer have a greater risk of infection compared with healthy individuals, and “frequent hospital visits may further increase the risk of contracting COVID-19 during the current pandemic, especially in immunocompromised older patients with poor functional status.” While the pandemic continues, they said, outpatient visits for patients with cancer should be minimized “without compromising adequate patient care.” Although same-day administration has not been studied in the context of the COVID-19 pandemic, the authors wrote, “these methods were successfully used before the COVID-19 pandemic and may provide risk-minimization opportunities.” Plus, same-day administration may have an added benefit: “Reducing patient visits can also reduce the workload for healthcare workers, who are currently overburdened and overworked because of COVID-19.”

The reviewers recommended that the pegfilgrastim administration method “should be based on the patient’s specific needs, while also considering mitigating factors, such as the economic burden associated with biologic medications and the risk of COVID-19.”

This article first appeared on The Center for Biosimilars® website.

REFERENCE

The CD3 receptor expressed on the surface of T cells, according to a release maturation antigen (BCMA) expressed on the surface of myeloma cells and disease had progressed on other types of therapy. Teclistamab (Tecvayli) for treatment of relapsed or refractory multiple myeloma, marking a new class of therapy now available for patients whose disease had progressed on other types of therapy. Teclistamab is a bispecific T-cell engager antibody that targets both B-cell maturation antigen (BCMA) expressed on the surface of myeloma cells and the CD3 receptor expressed on the surface of T cells, according to a release from Janssen. It is injected subcutaneously, and its approval is for adults with multiple myeloma who have received at least 4 earlier lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

The accelerated approval was based on the results of MajesTEC-1, a single-arm, multicenter phase 1/2 study (NCT03145181 and NCT04557098) involving 110 patients who had previously received at least 3 lines of therapy (including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody) but who had not yet received BCMA-targeted therapy. The median number of prior lines of therapy was 5, and 78% of patients had received 4 or more prior lines of therapy.

Investigators found an overall response rate of 61.8% (95% CI, 52.1%-70.9%) among these patients receiving teclistamab in the trial, and 28.2% of patients achieved a complete response or better. The effects were seen quickly, with a median time to first response of 1.2 months. These results were first reported at the American Society of Hematology Annual Meeting & Exposition in December 2021. The FDA’s approval of teclistamab comes with a boxed warning for cytokine release syndrome and neurologic toxicity, including immune effector cell–associated neurotoxicity syndrome. As such, the drug will be available only through a Risk Evaluation and Mitigation Strategies program.

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Other common adverse reactions occurring in at least 20% of patients were fever, musculoskeletal pain, injection site reaction, and fatigue. The most frequent grade 3 to 4 laboratory abnormalities were decreases in lymphocytes, neutrophils, white blood cells, hemoglobin, and platelets.

“As a clinician and researcher, I see firsthand the human toll of this incurable disease. The approval of teclistamab, as the first bispecific antibody in relapsed or refractory multiple myeloma, is a meaningful step in helping many of these hard-to-treat patients,” Ajai Chari, MD, professor of medicine at the Icahn School of Medicine at Mount Sinai, New York, New York, and an investigator on MajesTEC-1, said in the company’s news release.  

**REFERENCES**


**Combination of Tremelimumab and Durvalumab Approved by FDA for Unresectable Liver Cancer**

The FDA has approved a dual immunotherapy option of tremelimumab, sold as Imjudo, in combination with durvalumab, sold as Imfinzi, for the treatment of adult patients with unresectable hepatocellular carcinoma (HCC), the most common type of liver cancer. The drugs’ sponsor, AstraZeneca, announced the approval October 24, 2022.

This regimen includes a single 300-mg dose of the anticytotoxic T lymphocyte–associated antigen 4 antibody tremelimumab added to a 1500-mg dose of the anti–programmed cell death ligand-1 antibody durvalumab, followed by a 1500-mg dose of durvalumab every 4 weeks.

Approval is based on positive results from the phase 3 HIMALAYA trial (NCT03298451), presented in June 2022 at the American Society of Clinical Oncology annual meeting. Results showed that patients taking the tremelimumab/durvalumab regimen experienced a 22% reduction in risk of death compared with patients treated with sorafenib (HR, 0.78; 95% CI, 0.66-0.92; *P* = .0035).

Results appearing in *NEJM Evidence* showed that 31% of patients treated with the combination were still alive after 3 years, compared with 20% of patients treated with sorafenib at the point of follow-up. Both therapies are made by AstraZeneca, which announced the approval in a statement.

Liver cancer, the sixth most diagnosed cancer worldwide, is the fastest-rising cause of cancer death in the United States; an estimated 36,000 cases will be diagnosed in this country in 2022.

"Patients with unresectable liver cancer are in need of well-tolerated treatments that can meaningfully extend overall survival,” Ghassan Abou-Alfa, MD, MBA, attending physician at Memorial Sloan Kettering Cancer Center, New York, New York, and principal investigator in HIMALAYA, said in a statement. "In addition to this regimen demonstrating a favorable 3-year survival rate in the HIMALAYA trial, safety data showed no increase in severe liver toxicity or bleeding risk for the combination, important factors for patients with liver cancer who also have advanced liver disease.”

Andrea Wilson Woods, president and founder of Blue Faery: The Adrienne Wilson Liver Cancer Foundation, said that previously, patients living with liver cancer had few treatment options.

"With this approval, we are grateful and optimistic for new, innovative, therapeutic options. These new treatments can improve long-term survival for those living with unresectable hepatocellular carcinoma, the most common form of liver cancer. We appreciate the patients, their families, and the broader liver cancer community who continue to fight for new treatments and advocate for others.”
The safety profiles of the combination of Injudo added to Imfinzi and for Imfinzi alone were consistent with the known profiles of each medicine, and no new safety signals were identified. The most common adverse events (AEs) among patients with unresectable HCC in the trial were rash, diarrhea, fatigue, pruritis, musculoskeletal pain, and abdominal pain; 41% of patients receiving the combination in HIMALAVA reported serious AEs.◆

Cemiplimab previously demonstrated favorable efficacy as monotherapy compared with chemotherapy in the EMPower-Lung 1 trial, leading to its 2021 approval for advanced NSCLC with high PD-L1 expression (tumor proportion score ≥50%), and with no EGFR, anaplastic ALK, or ROS1 aberrations.

FDA Approves Cemiplimab/Chemotherapy Combo as First-line NSCLC Treatment

THE PD-L1 INHIBITOR CEMIPLIMAB (Libtayo) was approved in combination with platinum-based chemotherapy for the first-line treatment of adult patients with advanced non–small cell lung cancer (NSCLC) with no EGFR, ALK, or ROS1 aberrations, its manufacturer reported on November 8.1

The pivotal trial leading to the approval had been stopped early based on a recommendation by the independent data monitoring committee after the combination demonstrated a significant improvement in overall survival (OS), the primary end point.2

Patients must either have metastatic or locally advanced tumors that are not candidates for surgical resection or definitive chemoradiation, according to a statement from Regeneron Pharmaceuticals, and patients may be treated with this combination irrespective of PD-L1 expression or histology.1

The approval is based on data from a global phase 3 trial, EMPower-Lung 3, which investigated cemiplimab in combination with a physician’s choice of platinum-doublet chemotherapy (cemiplimab combination), compared with platinum-doublet chemotherapy alone.

The trial enrolled 466 patients with locally advanced or metastatic NSCLC, with no ALK, EGFR, or ROS1 aberrations, irrespective of PD-L1 expression or tumor histology.

Among those enrolled, 43% had tumors with squamous histology, 67% had tumors with <50% PD-L1 expression, 15% had inoperable locally advanced disease not eligible for definitive chemoradiation, and 7% had pretreated and clinically stable brain metastases.

Patients were randomized 2:1 to receive either cemiplimab 350 mg (n = 312) or placebo (n = 154) intravenously every 3 weeks, plus history-specific platinum-doublet chemotherapy.

Efficacy results comparing the combination therapy with chemotherapy alone showed:

- Median OS of 22 vs 13 months, representing a 29% relative reduction in the risk of death (HR, 0.71; 95% CI, 0.53–0.93; P = .014). The 12-month probability of survival was 66% for the cemiplimab combination vs 50% for chemotherapy, per Kaplan-Meier estimates.
- Median progression-free survival (PFS) of 8 vs 5 months, representing a 44% reduction in the risk of disease progression (HR, 0.56; 95% CI, 0.44–0.70; P < .0001). The 12-month probability of PFS for the cemiplimab combination was 38% vs 16% for chemotherapy.
- Overall response rate of 43% vs 23%.

Cemiplimab previously demonstrated favorable efficacy as monotherapy compared with chemotherapy in the EMPower-Lung 1 trial, leading to its 2021 approval for advanced NSCLC with high PD-L1 expression (tumor proportion score ≥50%), and with no EGFR, anaplastic ALK, or ROS1 aberrations.

Safety was assessed in 312 patients in the cemiplimab combination group (median duration of exposure, 38 weeks) and 153 patients in the chemotherapy group (median duration of exposure, 21 weeks).

The most common adverse events (AEs), occurring in >15% of patients, were alopecia (37% intervention vs 43% placebo), musculoskeletal pain (30% vs 36%), nausea (25% vs 16%), fatigue (23% vs 18%), peripheral neuropathy (23% vs 19%), and decreased appetite (17% vs 12%). Serious AEs occurred in 25% of patients, with treatment discontinuations due to AEs in 5% and fatal AEs in 6%.

The trial did not show any new safety signals.◆

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FDA Approves Mirvetuximab Soravtansine-gynx for Platinum-Resistant Ovarian Cancer

THE FDA GRANTED mirvetuximab soravtansine-gynx (Elahere; ImmunoGen) accelerated approval for adults with folate receptor α (FRα)–positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received 1 to 3 previous systemic treatment regimens.

The therapy is a FRα-directed antibody and microtubule inhibitor conjugate. It is the first antibody–drug conjugate approved for platinum-resistant disease.

“The approval of Elahere is significant for patients with FRα-positive platinum-resistant ovarian cancer, which is characterized by limited treatment options and poor outcomes,” said Ursula Matulonis, MD, in a statement.1 Matulonis is chief of the Division of Gynecologic Oncology at the Dana-Farber Cancer Institute, professor of medicine at Harvard Medical School, and co-principal investigator of SORAYA, the pivotal trial of mirvetuximab soravtansine-gynx.

“Elahere’s impressive anti-tumor activity, durability of response, and overall tolerability observed in SORAYA demonstrate the benefit of this new therapeutic option, and I look forward to treating patients with Elahere.”

The FDA also approved the VENTANA FOLR1 (FOLR-2.1) RxDx Assay as a companion diagnostic to determine which patients are eligible for mirvetuximab soravtansine-gynx.

The therapy was approved based on results from SORAYA (also known as Study 0417), a single-arm trial of 106 patients, all of whom had received bevacizumab as one of their previous regimens. However, the approval is for patients regardless of prior bevacizumab use. Using FOLR-2.1, patients were confirmed to have FRα-positive tumors.

Patients received 6 mg/kg (adjusted for ideal body weight) intravenously once every 3 weeks. In the study, the objective response rate was 31.7% (95% CI, 22.9%-41.6%) and the median duration of response was 6.9 months (95% CI, 5.6-9.7). Five patients had a complete response.

REFERENCES

The most common adverse events were vision impairment, fatigue, increased aspartate aminotransferase and alanine aminotransferase, nausea, keratopathy, abdominal pain, decreased lymphocytes, peripheral neuropathy, diarrhea, decreased albumin, constipation, increased alkaline phosphatase, dry eye, decreased magnesium, decreased leukocytes, decreased neurtrophils, and decreased hemoglobin.

Since mvretuxima sbrovstansine-gxyn was granted accelerated approval, continued approval may be contingent on verification and description of benefit in a confirmatory trial. Data from the confirmatory trial MIRASOL are expected in early 2023.

“Platinum-resistant ovarian cancer is a notoriously challenging disease to treat,” said Anna Berkenblit, MD, MMS, senior vice president and chief medical officer of Immunogen. “Given that there have been no new therapies approved by the FDA for this indication since 2014, Elahere's accelerated approval is a tremendous advance in the ovarian cancer treatment paradigm.”

REFERENCE


MANAGED CARE UPDATES

Medicare Fee Schedule Expands Access to Some Services but Cuts Physician Reimbursement 4.5%

CMS RELEASED THE 2023 Physician Fee Schedule (PFS) rule, which finalizes policies relating to telehealth; expands access to behavioral health care, cancer screening coverage, and dental care; and cuts reimbursement by 4.48%.

In the announcement of the final rule, the Biden administration touted the coverage expansions and that the final rule promotes innovation and coordinated care while aligning with the president’s Cancer Moonshot goal to cut the cancer death rate by at least 50% in the announcement of the final rule.

“Access to services promoting behavioral health, wellness, and whole-person care is key to helping people achieve the best health possible,” CMS Administrator Chiquita Brooks-LaSure, said in a statement. “The Physician Fee Schedule final rule ensures that the people we serve can achieve the best health possible and that our system provides timely, high-quality, and essential surgical care.”

However, at the very bottom of the announcement was one-third of ACOs.

“On balance, we believe this final rule will grow participation in accountable care organizations, which have already generated billions of dollars of savings for our health system,” he said in a statement.4 However, it wasn’t all compliments. Gaus noted concerns with the use of a prospectively projected administrative growth factor for ACO benchmarks or their spending targets, which NAACOS believes will harm more than one-third of ACOs.

“CMS should consider correcting the ‘rural glitch,’ where ACOs no longer benefit from the regional adjustment when lowering the spending of their assigned patients,” Gaus said. “This change would greatly help ACOs but remains in effect even after today’s changes.”

340B Program Payments

On the same day the PFS final rule was released, CMS also released the final rule of the Hospital Outpatient Prospective Payment System, which included payment for drugs acquired through the 340B program. CMS finalized a general payment rate of average sales price (ASP) plus 6%, which is a reversal from the payment of ASP minus 22.5% for calendar years 2019 through 2022.

The Community Oncology Alliance’s executive director, Ted Okon, MBA, called the final rule an “abdication of duty” regarding the health care system and patients.

“Just as President Biden seeks to make major efforts to reduce health care spending and lower the price of drugs, it is unbelievable that his administration will grossly overpay large health systems abusing the 340B Drug Pricing Program, which will cost Medicare seniors more out of pocket for their Medicare Part B drugs,” Okon said in a statement.2 CMS cited the Supreme Court’s unanimous decision in American Hospital Association v. Becerra, in which the court declared the reduction in yearly payments to hospitals as part of the 340B program unlawful. According to the decision, the reduced reimbursement rate could have been lawful if HHS had first conducted a survey of hospitals’ acquisition costs and set reimbursement rates based on those costs. Without
The analysis uses 2020 data for individuals with a commercial drug benefit tied to a medical benefit, as well as the PBMs used by insurers, to provide insight on PBM services performed for insurers. Five PBM services are reviewed: rebate negotiation, retail network management, claim adjudication, formulary management, and benefit design.

“The American Medical Association already has serious concerns about PBM business practices that can have a detrimental impact on patients’ access to and cost of prescription drugs,” AMA President Jack Resneck Jr, MD, said in a statement. “PBM markets require careful scrutiny as less competition and more vertical integration can embolden anti-competitive business practices to the detriment of patients.”

The analysis looked at enrollment in commercial drug insurance obtained directly from health insurers through health plans combining the medical and drug insurance benefits for the majority of Americans today. When PBMs were created, the goal was to contain drug spending by creating competition among substitute drugs. Manufacturers provide rebates to PBMs for favorable placement on the drug formulary, and PBMs are supposed to pass those rebates on to the insurer or employer.

“It is not clear whether PBMs are passing on those rebates,” the report notes. “Perhaps in response to this incomplete pass-through of rebates, health insurers have been vertically integrating with PBMs. As a result, the largest insurers in the country and even some smaller ones already have their own PBM or share the same owner with one.”

Although there is a large extent of vertical integration at the national level, the same is not necessarily true at the local level, according to the report. “In fact, most health insurers don’t have a national presence and instead operate at the local level as they are typically licensed to operate in a single state,” the report explains.

In Advanced NSCLC, Forgoing Treatment Leads to Increased Health Care Utilization

A NOTABLE PERCENTAGE of people with non–small cell lung cancer (NSCLC) go untreated for their cancers, and those patients tend to require more impatient and emergency department visits than people who receive cancer treatment, according to a new report.

The findings, which were presented recently at the Academy of Managed Care Pharmacy Nexus 2022 conference, offer new insights into the economic impacts of NSCLC treatment decisions.

Julie Vanderpoel, PharmD, MPA, of Janssen Scientific Affairs, and colleagues, noted that NSCLC represents up to 85% of all lung cancer cases. Although

The report highlights “a significant degree of vertical integration between health insurers and [pharmacy benefit managers].” The 8 largest insurers have a collective national market share of 61% and are affiliated with the 8 biggest PBMs.
In the current study, researchers wanted to know how the current treatment landscape for people with advanced cases of non-small cell lung cancer (NSCLC) translates into health care resource use and cost, both for individuals with NSCLC generally and for those who opt for or against treatment. They consulted claims databases of both commercial insurers and Medicare and Medicaid, and retrospectively analyzed patient costs both before and after a patient’s lung cancer diagnosis. The study included patients whose diagnosis came after January 1, 2015, in order to ensure the report reflected recent trends.

A total of 32,019 patients met all of the study’s inclusion standards, and 12,501 of those patients had advanced NSCLC. The patients had a mean age of 67.2 years and the advanced cohort had a mean age of 65.7 years. The mean baseline Quan-Charlson Comorbidity Index scores of participants was 2.1 for the entire cohort and 1.7 for the advanced NSCLC cohort. None of the patients had metastatic disease at baseline, per study protocols. During the 12-month pre-diagnosis baseline period, the participants had an average all-cause health care cost of $1857 per patient per month (PPPM), and those with advanced disease had index-period health care costs averaging $1387 PPPM.

Overall, 65% of patients in the study received treatment for their cancers over the average observation period of 13.3 months. About half (50.7%) of participants had observed metastatic disease during the postindex evaluation period, including 56% of individuals who received treatment and 40.7% of individuals who went untreated.

Among individuals with advanced cancers, 69.2% received treatment over a mean follow-up period of 9.5 months. Of those, 94.2% of treated patients and 100% of untreated patients reported metastatic disease.

For all patients, tumor removal surgery was the most common treatment. Among the advanced cohort, radiation therapy and antineoplastic therapy were most common.

The investigators found that the advanced NSCLC cohort had higher health care utilization. In both the overall and advanced cohorts, those who went untreated had higher rates of inpatient hospital stays, longer hospital stays, and higher numbers of emergency department visits, Vanderpoel and colleagues found.

Overall, patients had an average PPPM cost of $14,591, and those with advanced cases had an average cost of $22,350 PPPM. Among all patients, treated patients had costs just above the average ($15,050 PPPM), but untreated patients had slightly lower costs ($13,740), a reduction in spending attributable to lower pharmacy costs.

However, among patients with advanced cancers, treated patients had lower-than-average costs of $21,873 PPPM, whereas those who went untreated had PPPM costs of $23,196.

The authors said the increased hospital utilization of untreated patients, particularly those with advanced cancers, may be an indication of poorer quality of life in that population.

“These findings have important implications to population health decision makers regarding the value of innovative medications on the outcomes and quality of care for patients with advanced NSCLC,” the authors concluded.

## Risk of HCC Warrants Careful Surveillance in People With Primary Biliary Cholangitis

### PEOPLE WITH PRIMARY BILIARY CHOLANGITIS (PBC) and cirrhosis should be aggressively screened for hepatocellular carcinoma (HCC), using twice-annual liver screening, according to a new report in *Clinics in Liver Disease*.

The authors wrote about the latest evidence related to the risks and outcomes of HCC in people with PBC. They said such cases warrant vigilance. PBC is an autoimmune condition that affects the biliary epithelial cells, leading to a range of symptoms and severity, the authors noted. Some patients experience no symptoms, others develop cirrhosis, and some develop end-stage liver disease.

Another common complication of PBC, however, is HCC.

“Advanced fibrosis is the most important risk factor for the development of HCC, but there are other reports showing the development of HCC in PBC without evidence of advanced disease,” the investigators wrote.

They said autoimmune liver disease has been linked with an increased risk of developing HCC, but they said that risk is typically lower than the risk conferred by other liver diseases. Among autoimmune diseases, PBC appears to be associated with the greatest HCC risk. Among the research they cite, one study found people with PBC had an odds ratio (OR) of developing HCC of 31.33 (95% CI, 23.63-41.56), compared with primary sclerosing cholangitis (OR, 4.42; 95% CI, 2.06-9.45).

Although PBC cannot be cured at present, the investigators said treatment with ursodeoxycholic acid (UDCA) can delay progression to cirrhosis, and cirrhosis in PBC puts patients at a higher risk of developing HCC. However, there have been several studies looking at how UDCA itself affects the risk of HCC, and those studies have so far been inconclusive, the authors said.

Apparent risk factors for the development of HCC in people with PBC include age, the male sex, and comorbidities such as diabetes, previous viral infections, and alcohol consumption, they reported. They noted that even though PBC is more common in women than in men, studies indicate that women with PBC cirrhosis are less likely than men to develop HCC.

“The possible protective effect of estrogen against hepatocellular cancer through inhibiting cytokine and interleukin-6 has been proposed,” the investigators wrote.

What is clear, however, is that HCC is associated with a high risk of death. The 5-year survival rate among people with HCC and PBC is just 50%, significantly lower than the 75% HCC survival rate among people with other chronic
To decrease the incidence of chemotherapy-induced myelosuppression in patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen

SPARE THE MARROW.
COSELA HELPS PROTECT AGAINST MYELOSUPPRESSION,

COSELA™ (trilaciclib) helps protect hematopoietic stem and progenitor cells (HSPCs), the source of blood cell lineages, including neutrophils, red blood cells, and platelets

THE FIRST AND ONLY PROACTIVE MULTILINEAGE MYELOPROTECTION THERAPY

In the Pivotal Study in 1st-line ES-SCLC, COSELA administered before an etoposide/carboplatin + atezolizumab (E/P/A) regimen resulted in :

- **REDUCED INCIDENCE AND DURATION OF SEVERE NEUTROPENIA**
  - Primary Endpoints: 1.9% vs 49.1% (P<0.0001) and 0 days vs 4 days (P<0.0001) with and without COSELA, respectively*

- **NUMERICALLY LOWERED INCIDENCE OF GRADE 3/4 ANEMIA AND RBC TRANSFUSIONS**
  - Secondary Endpoints: 19% vs 28% and 13% vs 21% with and without COSELA, respectively†

- **REDUCED THE INCIDENCE OF GRADE 3/4 THROMBOCYTOPENIA**
  - Secondary Endpoint: 1.9% vs 37.7% with and without COSELA (P=0.0026)‡

- **REDUCED RATE OF CHEMOTHERAPY DOSE REDUCTIONS**
  - Secondary Endpoint: 2.1 vs 8.5 with and without COSELA (P=0.0195)§

**INDICATION**

COSELA is indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

*Multiplicity-adjusted P values. Adjusted relative risk (aRR) 0.038 (95% CI, 0.008, 0.195) and mean difference -3.6 (95% CI, -4.9, -2.3), respectively. Duration evaluated in Cycle 1.

†aRR 0.663 (95% CI, 0.336, 1.310) and aRR 0.642 (95% CI, 0.294, 1.404). RBC transfusions measured on/after 5 weeks. Grade 3/4 anemia defined as Grade 3/4 decreased hemoglobin.

‡Raw one-sided P value not adjusted for multiplicity. aRR 0.053 (95% CI, 0.008, 0.356). Results for platelet endpoints including incidence of Grade 3/4 thrombocytopenia and platelet transfusions were not consistent across COSELA clinical trials; in studies 2 and 3, no difference in the incidence of Grade 3/4 thrombocytopenia AEs was observed between the COSELA and placebo groups.

§Raw one-sided P value not adjusted for multiplicity. Rate of all-cause dose reductions, events per 100 cycles. aRR 0.242 (95% CI, 0.079, 0.742).

**References:**

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REVIEW MULTILINEAGE EFFICACY AT COSELA.COM
SELECT IMPORTANT SAFETY INFORMATION

CONTRAINICATION

• COSELA is contraindicated in patients with a history of serious hypersensitivity reactions to trilaciclib.

WARNINGS AND PRECAUTIONS

Injection-Site Reactions, Including Phlebitis and Thrombophlebitis

• COSELA administration can cause injection-site reactions, including phlebitis and thrombophlebitis, which occurred in 56 (21%) of 272 patients receiving COSELA in clinical trials, including Grade 2 (10%) and Grade 3 (0.4%) adverse reactions. Monitor patients for signs and symptoms of injection-site reactions, including infusion-site pain and erythema during infusion. For mild (Grade 1) to moderate (Grade 2) injection-site reactions, flush line/cannula with at least 20 mL of sterile 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after end of infusion. For severe (Grade 3) or life-threatening (Grade 4) injection-site reactions, stop infusion and permanently discontinue COSELA. Injection-site reactions led to discontinuation of treatment in 3 (1%) of the 272 patients.

Acute Drug Hypersensitivity Reactions

• COSELA administration can cause acute drug hypersensitivity reactions, which occurred in 16 (6%) of 272 patients receiving COSELA in clinical trials, including Grade 2 reactions (2%). Monitor patients for signs and symptoms of acute drug hypersensitivity reactions. For moderate (Grade 2) acute drug hypersensitivity reactions, stop infusion and hold COSELA until the adverse reaction recovers to Grade ≤1. For severe (Grade 3) or life-threatening (Grade 4) acute drug hypersensitivity reactions, stop infusion and permanently discontinue COSELA.

Interstitial Lung Disease/Pneumonitis

• Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with cyclin-dependent kinases (CDK)4/6 inhibitors, including COSELA, with which it occurred in 1 (0.4%) of 272 patients receiving COSELA in clinical trials. Monitor patients for pulmonary symptoms of ILD/pneumonitis. For recurrent moderate (Grade 2) ILD/pneumonitis, and severe (Grade 3) or life-threatening (Grade 4) ILD/pneumonitis, permanently discontinue COSELA.

Embryo-Fetal Toxicity

• Based on its mechanism of action, COSELA can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should use an effective method of contraception during treatment with COSELA and for at least 3 weeks after the final dose.

ADVERSE REACTIONS

• The most common adverse reactions (≥10%) were fatigue, hypocalcemia, hypokalemia, hypophosphatemia, aspartate aminotransferase increased, headache, and pneumonia.

To report suspected adverse reactions, contact G1 Therapeutics at 1-800-790-G1TX or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

This information is not comprehensive. Please see the Brief Summary of Prescribing Information on the adjacent page.
Table 1: Recommended Actions for Adverse Reactions as described in Table 1 [see Warnings and Precautions (5)]

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Recommended Action</th>
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</thead>
<tbody>
<tr>
<td>Dose Modification for Adverse Reactions</td>
<td><strong>Discontinuation of Treatment</strong></td>
</tr>
<tr>
<td><strong>Acute Drug Hypersensitivity Reaction</strong></td>
<td>- Stop infusion and permanently discontinue COSELA</td>
</tr>
<tr>
<td></td>
<td>- Hypokalemia: potassium decreased (lab) or TEAE preferred terms 'Hypokalemia,' 'Blood Electrolyte Abnormality'</td>
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<td></td>
<td>- Hypophosphatemia: phosphate decreased (lab) or TEAE preferred terms 'Hypophosphatemia,' 'Blood Electrolyte Abnormality'</td>
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<tr>
<td></td>
<td>- Thrombocytopenia: platelet count decreased (lab) or TEAE preferred term 'Thrombocytopenia'</td>
</tr>
<tr>
<td></td>
<td>- Hyperglycemia: increased plasma glucose level (lab) or TEAE preferred terms 'Hyperglycemia'</td>
</tr>
<tr>
<td></td>
<td>- Hyperkalemia: potassium increased (lab) or TEAE preferred terms 'Hyperkalemia'</td>
</tr>
<tr>
<td></td>
<td>- Hypocalcemia: calcium decreased (lab) or TEAE preferred term 'Hypocalcemia'</td>
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<tr>
<td></td>
<td>- Hypovolemia: decreased blood pressure (lab) or TEAE preferred term 'Hypovolemia'</td>
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<td></td>
<td>- Hypertension: increased blood pressure (lab) or TEAE preferred term 'Hypertension'</td>
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<tr>
<td><strong>ILD/Pneumonitis</strong></td>
<td>- ILD/Pneumonitis: increased lung density, new onset or worsening of ILD/Pneumonitis (lab) or TEAE preferred term 'ILD/Pneumonitis'</td>
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<td>- Hypophosphatemia: phosphate decreased (lab) or TEAE preferred terms 'Hypophosphatemia,' 'Blood Electrolyte Abnormality'</td>
</tr>
<tr>
<td><strong>Acute Kidney Injury</strong></td>
<td>- Acute Kidney Injury: increased serum creatinine (lab) or TEAE preferred term 'Acute Kidney Injury'</td>
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<td></td>
<td>- Hypokalemia: potassium decreased (lab) or TEAE preferred terms 'Hypokalemia,' 'Blood Electrolyte Abnormality'</td>
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</table>

**Table 4: Potentially Significant Drug Interactions with COSELA**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potentially Significant Drug Interactions with COSELA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cisplatin</strong></td>
<td>Closely monitor for QT interval prolongation and cause serious ventricular arrhythmias.</td>
</tr>
<tr>
<td><strong>Dofetilide</strong></td>
<td>Increased plasma levels of both cisplatin and doetilide may occur in patients who are also receiving COSELA.</td>
</tr>
<tr>
<td><strong>Etoposide</strong></td>
<td>Increased plasma levels of both cisplatin and doetilide may occur in patients who are also receiving COSELA.</td>
</tr>
<tr>
<td><strong>Hydroxyurea</strong></td>
<td>Use of COSELA is not recommended in patients with severe hepatic impairment.</td>
</tr>
</tbody>
</table>
liver diseases, the authors said. The best chance of survival for patients is liver transplant, they noted.

At present, the authors added, cirrhosis is the only indication for which all scientific societies recommend HCC screening. They said cirrhosis in PBC warrants screening every 6 months given the high risks associated with HCC, and they added that more studies are needed to better understand the ways in which treatment response for PBC might affect the risk of developing HCC.

**REFERENCE**


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Could Combining Use of BTK Inhibition, CAR T-Cell Therapy Yield Better Outcomes in MCL?

**AS CHIMERIC ANTIGEN RECEPTOR** (CAR) T-cell therapy and Bruton tyrosine kinase (BTK) inhibitors become cornerstones of treatment for advanced mantle cell lymphoma (MCL) in their own right, authors of an article in Current Oncology Reports say studies suggest the feasibility of combining the treatments for improved outcomes.

There are currently 3 approved BTK inhibitors in relapsed/refractory (R/R) MCL: first-generation ibrutinib (Imbruvica) and second-generation acalabrutinib (Calquence) and zanubrutinib (Brukinsa). In 2020, CAR T-cell therapy entered the MCL market with the approval of brexucabtagene autoleucel (Tecartus) in patients with R/R disease.

Although both categories have yielded impressive efficacy for some patients, there are a group of patients who don't achieve sufficient outcomes, including those who discontinue ibritinib due to treatment intolerance, develop resistance to BTK inhibitor treatment, and have short-lived responses to CAR T-cell therapy due to a variety of factors, including T-cell exhaustion.

"Evidence suggests that concomitant administration of BTKi and CAR T-cell therapy may provide a greater treatment benefit than either agent alone," noted the authors. "In vitro analyses demonstrate that stimulation of CAR T-cells with a BTKi enhances the Th1 response and T-cell effector activity by increasing cytokine production and cytolytic activity. In addition, exposure to a BTKi increases T-cell expansion, viability, and engraftment."

With the jury still out on whether sequential administration of BTK inhibitors and CAR T-cell therapy is more beneficial than concomitant use, the group outlined recommended scenarios each approach. For example, the researchers recommend CAR T-cell therapy be used ahead of BTK inhibition in BTK inhibitor-naïve patients with high-risk disease characteristics because they will likely not achieve durable responses to a BTK inhibitor. According to the researchers, in cases like this, a BTK inhibitor could be used as a bridge in patients who did not respond or who had a partial response to CAR T-cell treatment.

The researchers recommend use of a covalent BTK inhibitor, either as monotherapy or in combination with another treatment like venetoclax (Venclexta), in patients who don’t respond to or relapse following CAR T-cell treatment and have not previously received BTK inhibitor treatment. Noncovalent BTK inhibitors are recommended, either alone or in combination with another treatment, in patients who have previously been treated with a covalent BTK inhibitor.

The authors explained that to date, there is no approved option for concomitant use of CAR T-cell therapy and a BTK inhibitor—leading an absence of standardized guidelines for the treatment approach—although the approach may be feasible in patients who are naïve to both because a combination of the two may improve outcomes.

"Evidence supporting the use of concomitant BTKi and CAR T-cell therapy is mostly limited to studies in CLL, as patients with PBC typically have low rates of (complete response) with CAR T-cell therapy, likely due to CLL-induced T-cell dysfunction," explained the researchers. "In vitro studies suggest that ibrutinib may enhance CAR T-cell expansion and increase cell viability as well as improve cell engraftment, tumor clearance, and survival. Stimulation of CAR T cells with ibrutinib or acalabrutinib enhanced CAR T-cell effector function; prolonged BTKi stimulation further increased cytokine production and Th1 differentiation."

Drawing on the limited data available in CLL, the researchers suggest that a BTK inhibitor be used as bridging therapy and during lymphodepletion in preparation for CAR T-cell therapy. The group noted that using a BTK inhibitor directly following CAR T-cell therapy may lead to drug-drug interactions, off-target toxicity, and immunomodulatory effects. They added that although no published data have yet pointed to increased toxicity or reduced efficacy associated with concomitant use of a BTK inhibitor during lymphodepletion or immediately after CAR T-cell therapy, providers should closely monitor patients for related toxicities and other adverse events.

**REFERENCE**


Identifying ASCT-Ineligible Patients Who Could Benefit From CAR T-Cell Treatment

**RESEARCHERS OF A NEW PAPER** have characterized groups of patients with diffuse large B-cell lymphoma (DLBCL) who may benefit from chimeric antigen receptor (CAR) T-cell therapy despite not being eligible for autologous stem cell transplantation (ASCT), including older patients with more comorbidities.

Both ASCT and CAR T-cell therapy are intensive and potentially curative treatment options for patients with DLBCL. Due to a growing amount of real-world data, there have been suggestions that CAR T-cell therapy—currently approved for use after 2 lines of therapy in this setting—may be superior to ASCT in the second line for patients with relapsed or refractory disease. Data also suggest that the technology may be an option for patients who are not eligible for ASCT based on certain patient characteristics, prior treatments, stem cell availability, or tumor chemo-sensitivity.

"Real-world experience has shown that CAR T-cell therapy is feasible in patients who would not have been eligible for an ASCT. Thus, it is important to identify this ‘subtle but real’ population of patients who are ASCT ineligible but CAR T-cell eligible," wrote the researchers. "This population of patients will be further defined as we get more experience with CAR T-cell therapy. In particular, it will be important to improve our knowledge regarding treatment-related morbidity and mortality and, if possible, to develop scores capable of predicting the risk of severe/lethal toxicities (acute and delayed) after CAR T cells."

Their findings were published in the European Journal of Cancer.

Currently, 3 ongoing prospective trials—ALYCANTE (NCT04531046), TRANS-SCEND-PILOT-017006 (NCT03483103), and DALY 2-EU (NCT04844866)—are assessing CAR T-cell treatment in the second line for patients not eligible for ASCT. The researchers of the paper in European Journal of Cancer highlighted the importance of identifying such patients to promote optimal use of CAR T-cell treatments.

For example, ASCT is typically offered in younger patients with fewer comorbidities, whereas CAR T-cell treatment has emerged as a safe option in less fit patients.
patients and those who are older. Typically, patients older than 65 to 75 years and patients with intermediate performance status, mild organ dysfunction, or mild comorbidities are not eligible for transplant. However, real-world data have suggested that CAR T-cell therapy may be an option. The group noted that although each institution has its own definition of eligibility for both treatment approaches, eligibility is typically more flexible for CAR T-cell treatment.

The researchers also cited prior treatment as a consideration. Although a patient who previously received ASCT would not be eligible for the procedure again, they would be eligible for CAR T-cell therapy.

Another example outlined by the researchers is in a case when stem cell collection was not successful, thus inhibiting the ability for a transplant but still allowing for feasible CAR T-cell treatment. According to the researchers, in these patients, there is a more than 95% success rate in leukapheresis and CAR T-cell manufacturing.

Chemosensitivity is also a consideration because patients who are refractory to salvage chemotherapy would not benefit from high-dose chemotherapy followed by ASCT. However, due to the unlikelihood of cross-resistance, immunotherapy treatment with CAR T cells would be viable.

REFERENCE
Vu S, Lemoine J, Armand P, Lemoine F, Houot R. Transplant-ineligible but chimeric antigen receptor T-cells eligible: a safer choice due to compatibility from use of the patient's own cells, there are autologous and allogeneic sources. Although autologous transfer is considered the gold standard, the researchers explained, CAR NK-cell therapy, is explained the researchers, is outlined the potential of CAR natural killer (NK) cell–based treatment in oncology.

CAR NK cells have been heavily assessed as a source for NK-cell adoptive transfer therapy. Allogeneic NK cells can be obtained from peripheral blood, umbilical cord blood, pluripotent stem cells, and commercially available NK cell lines such as NK-92. The authors wrote, “They can provide an off-the-shelf option that can reduce manufacturing costs and dose escalation protocols and make reproducibility much easier.”

According to the researchers, allogeneic alloreactive NK cells offer a protective role against GVHD similar to that seen with CAR NK-cell therapy. The reason for this protective capacity, explained the group, is the ability of NK cells to work in a non–antigen-specific way and to regulate immune cells typically involved in the GVHD process.

REFERENCE

Organ Transplant Patients at Higher Risk of BCC vs the General Population

DEVELOPMENT AND PROGRESSION of basal cell carcinoma (BCC) were more common among organ transplant recipients (OTRs) compared with the general population, and the former also had a higher rate of deep invasion, according to new study findings published in Archives of Dermatological Research.

The study authors noted that their data point to immunosuppression as the culprit, which echoes previous research and highlights the greater skin cancer risk these patients face.

“The most frequently occurring skin cancers in OTRs are squamous cell carcinomas (SCCss), and because they are responsible for high morbidity and mortality, SCCs in OTRs have been studied extensively,” the investigators wrote. “BCCs occur less frequently than SCCs and rarely metastasize, and thus BCCs in OTRs have received relatively little attention despite their increased incidence compared with the general population.”

Data for their analysis were provided by histopathology reports from 2 prospective skin cancer studies, 1 among the general population (QSkin Sun and Health Study) and 1 among OTRs (Skin Tumors in Allograft Recipients). These data were on BCC tumor site, size, level of invasion, subtype, and biopsy procedure. Age- and sex-adjusted prevalence ratios were also examined.

Overall, prevalence results show an average of 3.51 cases of BCCs per OTR, or 702 BCCs from among 200 OTRs. This rate was significantly higher than the 2.15 BCC cases per general population, or 1725 BCCs seen in 804 cases. Cases were more often seen among male patients in both groups, but men accounted for more of the OTRs vs general population cases: 76% vs 56%. In addition, among the OTR group, more than twice as many patients with BCC had their skin checked more than once each year: 53% vs 21%.

No matter the biopsy method—excision, punch/shave biopsy, or curettage, respectively—the head/neck region was the most common site for a BCC among both patient cohorts: 46.4% and 41.9% in the OTR group and 43.4% and 33.4% in the general population. Excision was the most common surgical method overall for tumors of 2 cm or smaller, but tumor size data were lacking from a sizeable portion of each group who had punch/shave biopsy or curettage: 75.5% of the OTR group and 67.1% of the general population group.

The authors noted this is because, “substantial proportions of BCC tumors in each group were diagnosed and treated only by partial biopsies, thus tumor...
size and depth of invasion were unknown for over two-thirds of partially excised BCCs in both case groups.”

There were also more instances of unknown tumor depth in the OTR group, but this group also had a higher rate of nonaggressive tumors for those who underwent excision vs the general population patients: 82.0% vs 68.6%, respectively. Nonaggressive rates were similar for punch/shave biopsy or curettage, at 83.1% and 83.2%, respectively. Aggressive tumor results were more often seen in the general patient excision cohort (31.4%) compared with the OTR excision cohort (18.1%).

A greater number of higher-risk BCCs per person were seen in the OTR group, among whom more tumors were larger and invaded skin beyond the dermis layer:

- Higher-risk BCCs were seen in 327 per 128 cases in the OTR group vs 703 per 457 cases in the general population group.
- Tumors 2 cm or larger were seen in 7% of the OTR group vs 4% in the general population group.
- Cancers invading beyond the dermis occurred in 5% of the OTR patients vs 2% of the general population group.

Adjusting for age and sex produced higher prevalence ratios for BCCs on the scalp or ear, higher-risk BCCs that were 2 cm or larger, and BCCs that extended beyond the dermis among the OTR group compared with the general population.

“This is among the largest clinicopathological series of BCCs in OTRs reported to date and one of the few to compare BCCs in OTRs and the general population,” the authors concluded. “Patient care and future research to confirm these findings may both benefit from enhanced communication between treating clinicians and dermatopathologists not only via the pathology requisition but also by comprehensive histopathologic reporting of BCCs.”

Nonmelanoma skin cancers removed with surgery are typically on the head and neck due to UV light exposure, and incomplete excision rates have been reported to be 10% to 17%, the authors noted, with higher rates for periorbital excisions.

There are many risks with incomplete excision in skin cancer, including recurrence requiring additional treatment. “In cosmetically sensitive areas,” the authors wrote, “the aesthetic outcome sometimes overshadows the aim of oncological clearance, and so as little tissue is removed as possible to minimize the defect size though compromising on the oncological margin.”

The odds ratio of incomplete excision when guided by dermoscopy was 0.29 (95% CI, 0.25-0.34). Heterogeneity was assessed, and the P statistic was found to be 0%. Of note, all 6 studies found that dermoscopy improved the likelihood of complete excision.

To the authors’ knowledge, “this is the first systematic review that has focused on the comparison of dermoscopy as an intervention in marking of surgical margins to determine the primary outcome of incomplete excision rate.”

Nonmelanoma skin cancers removed with surgery are typically on the head and neck due to UV light exposure, and incomplete excision rates have been reported to be 10% to 17%, the authors noted, with higher rates for periorbital excisions.

There are many risks with incomplete excision, including recurrence requiring additional treatment. “In cosmetically sensitive areas, the aesthetic outcome sometimes overshadows the aim of oncological clearance, and so as little tissue is removed as possible to minimize the defect size though compromising on the oncological margin,” the authors wrote.

Despite the low cost and availability of dermoscopy, the authors noted that training is limited outside the field of dermatology. With more patients likely to present with skin lesions, however, the authors recommended that more physicians be trained in dermoscopy, especially surgeons.

“We would recommend that dermatoscopes be routinely available and used in operating departments, that training in their use be provided for surgeons, and that measurement of excision margins, along with the use or otherwise of dermoscopy, be recorded to aid future analysis of the utility of dermoscopy,” they wrote.

**REFERENCE**

For many patients with PNH
THE STRUGGLE CONTINUES
They are experiencing hemolysis, anemia,
and the burden of infusions

References:
For many patients with PNH
THE STRUGGLE CONTINUES
They are experiencing hemolysis, anemia, and the burden of infusions\textsuperscript{1,2}

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Navigating the Complexities of Frontline Immunotherapy in Non–Small Cell Lung Cancer

ALIA C. LYNCH, PHARMD, BCOP

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Navigating the Complexities of Frontline Immunotherapy in Non–Small Cell Lung Cancer

Role of Genomic Tumor Testing in Patients Being Considered for Treatment With Immunotherapy

Overview of Non–Small Cell Lung Cancer

IN THE UNITED STATES, lung cancer is the third most common type of cancer, representing 12.3% of all new cancer cases, and is the leading cause of cancer-related death. Approximately 236,740 new lung cancer cases, 117,910 men and 118,830 women, will be diagnosed in 2022, leading to 130,180 deaths.1 Lung cancer is most commonly diagnosed in people aged 65 to 74 years, with a median age of diagnosis of 71 years. The 5-year overall survival (OS) for lung cancer is estimated at 21.7%; however, most patients are diagnosed with distant disease, which has a 5-year OS of less than 10%.2 There are 2 main histological types of lung cancer: small cell lung carcinoma (SCLC), which makes up 15% of all lung cancers, and non–SCLC (NSCLC), which makes up 85% of all lung cancers. NSCLC is further classified as adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma.3 Development of lung cancer is multifactorial, involving numerous genetic and epigenetic variations, specifically enhanced growth pathway activation and inhibition of tumor suppressor pathways. Recently, advancements in molecular biology of lung cancer have led to a shift in the lung cancer treatment paradigm with hopes that this revolution may improve patient outcomes in this disease with a historically poor prognosis.4

Risk Factors and Pathophysiology

Historically, cytotoxic chemotherapy was the primary treatment modality for advanced-stage disease. Research has shown that low immunogenicity, antigen modulation, and tumor-induced immune suppression of lung cancer lead to treatment resistance through tumor immune escape. This has led to further discovery of how the immune system can be harnessed as a treatment modality, more specifically the role of immune checkpoint inhibition. The antitumor immune response is initiated through tumor antigen recognition by T lymphocytes, followed by T-cell receptor costimulatory binding to peptide-major histocompatibility complex on antigen-presenting or cancer cells. Expressed on activated T cells is programmed cell death-1 protein (PD-1), an immune checkpoint receptor. Expressed on antigen-presenting cells or tumor cells are programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2). T-cell inactivation by tumor cells occurs when PD-L1 or PD-L2 interacts with the PD-1 receptor on the activated T cell (Figure 1). This mechanism of immune escape can be reversed through PD-1 or PD-L1 inhibition with novel checkpoint inhibitors.5

Roles and Recommendations for Biomarkers in Non–Small Cell Lung Cancer

Biomarker testing has transformed the treatment paradigm for NSCLC, and with approximately 60% of patients with NSCLC having an oncogenic driver mutation, it is essential that this testing is efficiently and effectively performed.6 Biomarkers present in tissue and/or blood can be divided into 2 main categories: predictive or prognostic. Predictive biomarkers are those that can be targeted with a specific therapy to influence patient outcomes (eg, EGFR exon 19 deletion or PD-L1 expression). Prognostic biomarkers are markers that impact patient survival but cannot be influenced by therapy (eg, most KRAS mutations [except for G12C]).7

Precision oncology in NSCLC has been rapidly evolving, thus requiring careful interpretation of guideline recommendations.8 Presently, PD-1 expression is the most optimal biomarker to determine if patients are candidates for PD-1/PD-L1 inhibitor therapy. The National Comprehensive Cancer Network (NCCN) recommends (category 1) immunohistochemical (IHC) testing for PD-L1 expression in patients with metastatic NSCLC prior to initiation of first-line treatment. Several scoring systems exist to identify the proportion of tumor cells expressing membranous staining at any level: the tumor proportion scoring (TPS) counts the number of positive and negative PD-L1–staining cells; the combined positive score divides the number of PD-L1–positive cells by the number of total tumor cells; and tumor-infiltrating immune cells (IC) might add a predictive value for benefit of a specific therapy.2,9,10 As shown in Table 1,11-12,13 distinctive anti-PD-L1 IHC companion diagnostic assays have been created for each individual immunotherapy. Each assay has been analytically and clinically validated to support safe and effective use of its associated immunotherapy agent. It is important to note that quantitative PD-L1 positivity or negativity of a tumor sample vary between antibody and test used.2

While PD-L1 expression testing is recommended prior to first-line treatment, many challenges exist which impact the utility of PD-L1 expression as a predictive biomarker. First, immunohistochemistry testing requirements and practices vary among the study design of the immunotherapy-containing clinical trials. Trials also differ in type of PD-L1 assay used, numerical PD-L1 expression criteria, whether tumor or IC types are used or fresh or archival tissue.15 In addition, PD-L1 expression heterogeneity within biopsy and surgically resected samples has been demonstrated; such variability poses a problem for pathologists and clinicians when interpreting these results.16 Another hurdle stems from the fact that PD-L1 expression is impacted by numerous in vitro modalities and other ICs in the tumor microenvironment; therefore, the capability of enforcing immunogenicity may be inconsistent among tumors.15 Additionally, current assays lack standardization.15 Furthermore, because PD-L1 expression has temporal and spatial heterogeneity, overall expression can be distorted from previous treatments.15 Lastly, some patients with PD-L1 expression may not respond, yet some...

**FIGURE 1.** T-Cell Inactivation Versus Activation Through PD-1 and PD-L1 Pathway

<table>
<thead>
<tr>
<th>TUMOR CELL</th>
<th>INACTIVE T CELL</th>
<th>TUMOR CELL</th>
<th>ACTIVE T CELL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1</td>
<td>PD-L1</td>
<td>PD-1</td>
<td>PD-L1</td>
</tr>
</tbody>
</table>

PD-1, programmed cell death-1 protein; PD-L1, programmed death-ligand 1.

responses may occur in patients with negative PD-L1 expression.24
Other alternative biomarkers have been under investigation for use in NSCLC. Two of particular interest include tumor mutational burden (TMB) and tumor infiltrating lymphocytes (TILs).13 TMB is described as the number of mutations per megabase of DNA.13 Recent data have questioned the relationship between TMB and immunotherapy response; thus, the NCCN guidelines removed TMB as an emerging biomarker for patients with metastatic NSCLC in 2020 given these concerns.2,18 In contrast, TILs have maintained status as a biomarker of interest in the immunotherapy landscape. TILs consist of all lymphocytic population-intruding tumor tissue, mainly CD4- and CD8-positive T cells. Increased TIL density is thought to be more reflective of immune recognition in tumor cells and indicate a T-cell-inflamed environment that may be more responsive to checkpoint blockade, inferring that TILs may have a prognostic biomarker role for immunotherapy.13 Data have proven the prognostic role of TILs in a multitude of tumor types and that PD-L1 expression was significantly correlated with intratumoral T-cell infiltration in NSCLC. Additional biomarker investigation would reassure adequate patient selection and predictability of anti-PD-L1/PD-L1 treatment response.20,21

Economic and Logistical Considerations of Biomarker Testing
Despite the growth of this area and strong endorsement of biomarker testing by health care entities, the financial implications and payer coverage exist as obstacles to testing. In 2018, the US Centers for Medicare & Medicaid Services approved a national coverage verdict that allows for the use of next-generation sequencing (NGS) testing in those with advanced NSCLC. The FDA has also consistently approved several NGS-based platforms for molecular testing in advanced cancer types, though appropriate coverage across private payers may be inconsistent. Instead of a single broad panel, many biomarker tests are executed through a sequence of single-gene tests.8 Among 5 US-based studies reporting economic impact of sequential versus frontline NGS testing strategies, two found that tumor tissue NGS, compared with sequential exclusionary or hotspot panel testing (discounting treatment costs), was cost-saving. One reported NGS upfront had the shortest turnaround time, quicker initiation of targeted treatment, and lower overall costs. Two studies found that NGS compared with single-gene testing was coupled with increased budget, though that was equalized by known cost-effectiveness for NGS.22 As more biomarkers materialize, it may be economical to shift toward a broad NGS-based assay.8

The significance of biomarker testing in NSCLC is clinically undisputable, yet there is inconsistent utilization in practice. While biomarker-based therapies are widely available, lack of satisfactory testing in the community oncology setting is a major concern and signifies that not all patients receive or have access to the most optimal upfront treatment.23 Previously reported data describe low rates of PD-L1 expression testing in US community-based oncology practices for patients with NSCLC. Many patients were not tested using companion diagnostics yet still received immunotherapy: others tested negative and also received immunotherapy.14 In 1 recent real-world, community setting study, patterns showed that 23.6% of patients were not tested for any biomarker (PD-L1 or driver mutation) at any point during the study, and only 49% had testing completed prior to first-line therapy.20 Both studies highlight a neglected opportunity to prescribe the most efficacious biomarker-directed frontline therapies and the importance of health care professional education regarding PD-L1 testing tactics for immunotherapy use.11,12 Reflex testing rather than awaiting a physician order has been proposed to help diminish the turnaround time to treatment initiation.4

Foundations of Evidence for the Use of FDA-Approved and Pipeline Immunotherapy Strategies for Frontline Treatment of NSCLC
Treatment recommendations for advanced NSCLC are first stratified based on the presence or absence of actionable oncogenic driver mutations. Targetable genes with FDA-approved first-line targeted therapies include EGFR, ALK, ROS1, BRAF, NTRK, MET, and RET.2,20 Those with actionable oncogenic drivers should receive the appropriate targeted therapy for their specific oncogene, regardless of PD-L1 expression, as targeted therapies generate greater response rates and generally have improved tolerability profiles when compared with chemotherapy and/or immunotherapy.2 If molecular testing is not possible, then it is recommended that patients be treated as if they do not have any actionable driver oncogenes.2

Those without an actionable oncogenic driver are categorized into 3 groups based on PD-L1 expression: PD-L1 greater than or equal to 50%, 1% to 49%, and less than 1%. Treatment options include single-agent immunotherapy, combination immunotherapy, and combination chemotherapy plus immunotherapy. In addition to PD-L1 expression, disease-specific (ie, histology, tumor burden) and patient-specific (ie, performance status, comorbidities) parameters drive treatment selection. Chemotherapy alone may be indicated as immunotherapy-based treatment regimens are contraindicated in patients with a history of active or severe autoimmune disease, history of solid organ transplantation, or in the presence of an oncogene driver alteration where lack of benefit is expected.2

Pembrolizumab, atezolizumab, or cetirizilimab as single agents are category 1, preferred recommended agents as first-line treatment options for eligible patients with metastatic NSCLC regardless of histology, greater than or equal to 50% PD-L1 expression levels, and negative test results for actionable driver mutations: pembrolizumab is also a first-line recommendation for PD-L1 expression of 1% to 49% (Table 24,49).

First-Line, Single-Agent Immunotherapy With PD-L1 Expression Greater Than or Equal to 50% for Advanced or Metastatic NSCLC
In May 2020, the FDA approved nivolumab plus ipilimumab as first-line treatment for patients with metastatic NSCLC with PD-L1 greater than or equal to 1% with no EGF or ALK genomic tumor aberrations (Table 31,40). The NCCN guidelines recommend nivolumab plus ipilimumab as category 1 for those with PD-L1 levels greater than or equal to 1%. Notably, nivolumab plus ipilimumab is also a recommended regimen for those with PD-L1 levels less than 1% and suggested as a reasonable option for patients with PD-L1 greater than 1% and concomitant renal impairment, in which chemotherapy may not be feasible.2

First-Line Dual Immunotherapy With PD-L1 Expression Greater Than or Equal to 1% for Advanced or Metastatic NSCLC
Combination nivolumab and ipilimumab with 2 cycles of platinum-doublet chemotherapy depending on histology, followed by nivolumab and ipilimumab maintenance until disease progression for first-line treatment in NSCLC without targetable tumor aberrations was FDA approved and is an NCCN category 1 recommendation for all histologies.2 Combination durvalumab and tremelimumab with platinum-based chemotherapy is FDA approved for all histologies of NSCLC without sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase genomic tumor aberrations (Table 431,45).

Pembrolizumab in combination with chemotherapy and atezolizumab in combination with bevacizumab, carboplatin, and paclitaxel is recommended as a category 1, preferred regimen for first-line treatment in those with metastatic NSCLC and negative actionable driver mutations, irrespective of PD-L1 expression (Table 54,26,48). Recently, the FDA approved cemiplimab in combination with platinum-based chemotherapy for this patient population, but guidelines at time of print had not been updated to reflect this new indication (Table 74,26).

Interestingly, neither atezolizumab combination is approved for use in SCC NSCLC, as the addition of nab-paclitaxel and carboplatin to atezolizumab in IMpower131 exhibited enhanced progression-free survival (PFS) but not OS in those with SCC NSCLC.46

TABLE 1. Companion Diagnostic Immunotherapy Assays for Frontline Treatment in Advanced NSCLC11,12

<table>
<thead>
<tr>
<th>Single/dual immunotherapy regimens for advanced NSCLC</th>
<th>IHC assay</th>
<th>IHC numerical value requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab monotherapy</td>
<td>PD-L1 IHC 22C3 phmDX (Agilent)</td>
<td>TPS ≥ 1%</td>
</tr>
<tr>
<td>Cemiplimab monotherapy</td>
<td>PD-L1 IHC 22C3 phmDX (Agilent)</td>
<td>TPS ≥ 50%</td>
</tr>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>PD-L1 IHC 28-8 phmDX (Agilent)</td>
<td>TPS ≥ 1%</td>
</tr>
<tr>
<td>Atezolizumab + monotherapy</td>
<td>Ventana PD-L1 (OP412 assay Ventana Medical Systems)</td>
<td>TC ≥ 1% or IC ≥ 10%</td>
</tr>
</tbody>
</table>

IHC, immunohistochemical; NSCLC, non–small cell lung cancer; PD-L1, programmed death-1; TC, tumor cell; TPS, tumor proportion scoring.
Adequate maintenance therapy selection depends on numerous considerations, such as histologic subtype, mutations, or gene status, performance score, and previous toxicity. The duration of maintenance therapy is typically dependent on the agent being used, with some stopping at the 24-month mark and others continuing until disease progression or unacceptable toxicity. Before the era of immunotherapy, pemetrexed was studied as switch maintenance in nonsquamous histology. Compared with best supportive care, pemetrexed improved PFS at 4.3 months compared with 2.6 months (HR, 0.50; P = .0001) and OS of 13.4 months versus 10.6 months (HR, 0.79; P = .012). While this strategy is becoming more obsolete, it may still serve a role in patients who are candidates for chemotherapy only regimens.

The concept of continuation maintenance was initially presented in the PARAMOUNT trial, in which patients with nonsquamous, nonprogressive NSCLC who completed 4 cycles of cisplatin/pemetrexed were then randomized to pemetrexed maintenance versus placebo. This led to a median PFS of 4.1 months for pemetrexed versus 2.8 months for placebo, a statistically significant reduction in death of 22% (HR, 0.78; P = .0195) and a 3.9 month
TABLE 5. Combination Chemotherapy plus Pembrolizumab Regimens and Trial Characteristics

<table>
<thead>
<tr>
<th>Trial/patient population</th>
<th>KEYNOTE-021</th>
<th>KEYNOTE-189</th>
<th>KEYNOTE-407</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-021</td>
<td>N = 123</td>
<td>N = 616</td>
<td>N = 559</td>
</tr>
<tr>
<td>Stratified based on PD-L1 expression ≤1% or &gt;1%</td>
<td>Treatment naive</td>
<td>Treatment naive</td>
<td>Treatment naive</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>Non–squamous</th>
<th>Non–squamous</th>
<th>SCC</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Pembrolizumab + carboplatin + pembrolizumab for 24 months and optional indefinite pembrolizumab maintenance vs carboplatin + pembrolizumab followed by optional indefinite pembrolizumab maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results</td>
<td>1-year OS was 62.9% vs 49.4% (P &lt; .001)</td>
</tr>
</tbody>
</table>

OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SCC, squamous cell carcinoma.

TABLE 6. Combination Chemotherapy plus Atezolizumab Regimens and Trial Characteristics

<table>
<thead>
<tr>
<th>Trial/patient population</th>
<th>IMpower150</th>
<th>IMpower130</th>
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<tbody>
<tr>
<td>N = 1202</td>
<td>N = 724</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>Non–squamous</th>
<th>Non–squamous</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Atezolizumab + carboplatin plus paclitaxel (ACP) vs bevacizumab + carboplatin + paclitaxel (BCP) vs atezolizumab + BCP (ABC) for 4–6 cycles followed by maintenance with atezolizumab, bevacizumab, or both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results</td>
<td>Median OS was 18.6 months vs 13.9 months (HR, 0.79; P = .023)</td>
</tr>
</tbody>
</table>

OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

TABLE 7. Combination Chemotherapy plus Cemiplimab Regimens and Trial Characteristics

<table>
<thead>
<tr>
<th>Trial/patient population</th>
<th>EMPOWER-Lung 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 466</td>
<td>Treatment naive</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>Non–squamous and SCC</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cemiplimab + platinum doublet chemotherapy (with either pembrolizumab or paclitaxel) every 3 weeks for 4 cycles, followed by cemiplimab + pembrolizumab maintenance if initially assigned to receive a pembrolizumab-containing regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results</td>
<td>ORR = 43.3% vs 22.7%</td>
</tr>
</tbody>
</table>

OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SCC, squamous cell carcinoma.

Improvement in OS in patients who received pembrolizumab maintenance. Subsequent studies evaluated bevacizumab alone and combination pembrolizumab and bevacizumab maintenance regimens, with both strategies showing improved PFS and OS. In recent years, continuation maintenance therapy has become standard of care and incorporated as such into clinical trial design. All immunotherapy and chemotherapy plus immunotherapy trials involve continuation maintenance in both patients with squamous and nonsquamous NSCLC.

As summarized in Table 8, depending on the first-line therapy used for nonsquamous NSCLC, NCCN guidelines recommend continuation maintenance using atezolizumab (category 2A), atezolizumab/bevacizumab (category 1), bevacizumab (category 1), cemiplimab (category 1), cemiplimab (category 1), pembrolizumab (category 1), pembrolizumab/pemetrexed (category 1), or pemetrexed (category 1). Pemetrexed use for switch maintenance therapy is a suggested option for patients with nonsquamous NSCLC. The use of gemcitabine maintenance is endorsed as a category 2B in NCCN guidelines due to minimal data demonstrating benefit. Based on first-line therapy used in patients with SCC NSCLC, guidelines recommend continuation maintenance therapy with atezolizumab, cemiplimab (category 1), nivolumab/platinumb (category 2A), pembrolizumab (category 1), pembrolizumab/pemetrexed (category 1), or pemetrexed (category 1).

Duration of immunotherapy

Data are scarce regarding optimal immunotherapy duration in various disease states, including NSCLC. There has been variation among clinical trials evaluating immunotherapy in advanced NSCLC, with some studies limiting immunotherapy use a maximum of 2 years and others allowing immunotherapy to continue until disease progression or unacceptable toxicity. Retrospective studies have found that there are a portion of patients who maintain long-term disease control despite early discontinuation of immunotherapy secondary to toxicity, raising the question of whether all responders need long-term maintenance.

CheckMate 153 was a community-based phase 3b/4 study assessing the impact of 1-year fixed-duration compared with continuous therapy on the efficacy and safety of nivolumab. Patients receiving nivolumab monotherapy were randomly assigned to continue nivolumab until disease progression/unacceptable toxicity or stop nivolumab at 1-year fixed duration with the ability to resume on-study retreatment after progression. Median PFS was longer in the continuous group compared with the fixed-duration group at 24.7 months versus 9.4 months, respectively (PFS population; HR, 0.56). Median OS was shown to be longer in the continuous group compared with the fixed-duration group (PFS population, not reached vs 32.5 months; HR, 0.61; intent-to-treat population, not reached vs 28.8 months; HR, 0.62).

In summary, it is evident that more research is needed to determine the optimal duration of
immunotherapy, as some patients may have disease progression despite long-term immunotherapy use and others may have long-term disease control after early discontinuation due to toxicity. This paradox has prompted further investigation into other biomarkers, such as minimal residual disease, that may help further our understanding.13

**Future Directions**

**COMBINATION CHEMOTHERAPY/IMMUNOTHERAPY**

Evolving frontline investigational tactics are necessary for the advancement of NSCLC treatment. Tislelizumab is a monoclonal antibody with high binding affinity to the PD-1 receptor and was engineered to decrease Fcγ receptor binding on macrophages, thus nullifying antibody-dependent phagocytosis, a possible mechanism of resistance to anti-PD-1 therapy. Tislelizumab was studied in a randomized phase 3 trial, RATIONALE-307, which contained untreated, histologically confirmed patients with stage IIIIB/IV SCC NSCLC. Patients were randomized to receive either tislelizumab in combination with paclitaxel and carboplatin (arm A), tislelizumab with nab-paclitaxel and carboplatin (arm B), or paclitaxel plus carboplatin alone (arm C). At a follow-up of 8.6 months, PFS was significantly greater with tislelizumab plus chemotherapy at 7.6 months in arm A and 7.6 months in arm B compared with 5.5 months in arm C. There was no impact of PD-L1 expression observed on PFS or ORR. These results indicate that tislelizumab plus chemotherapy may be an adequate first-line therapy in those with advanced SCC NSCLC. Results are also promising for use in nonsquamous NSCLC in the RATIONALE-304 trial.14 The ongoing TROPiCON-Lung02 phase 1b trial showed early results of datopotamab deruxtecan plus pembrolizumab with or without platinum chemotherapy, validating favorable activity and safety profile in those with untreated or pretreated, advanced or metastatic NSCLC lacking actionable genomic alterations. At the interim analysis, the ORR in the overall population was 37% in those treated with datopotamab deruxtecan and pembrolizumab and 41% in those receiving datopotamab deruxtecan plus pembrolizumab and platinum chemotherapy. Datopotamab deruxtecan offers a novel mechanism of action, as no Trop2-directed agents are currently FDA approved for NSCLC treatment.56

**COMBINATION IMMUNOTHERAPY/ TARGETED THERAPY**

Part 1 of the LEAP-006 trial was an open-label, safety run-in portion of the study where 12 patients received leovistinib 8 mg daily plus pembrolizumab every 3 weeks, with platinum-based chemotherapy given every 3 weeks for 4 cycles. Part 1 showed preliminary results of a 69.2% ORR.57

The LUX-Lung10 trial will assess the efficacy of afatinib plus pembrolizumab in patients with locally advanced or metastatic SCC NSCLC who progressed during or after first-line platinum-based treatment.58,59

Lastly, while atezolizumab is currently approved for intravenous use, a new, subcutaneous product in combination with recombinant human hyalurondase used for dispersion and absorption is being investigated to decrease treatment burden and ameliorate health care logistics. A phase 1b trial has demonstrated acceptable tolerability, and final results from the DMCin001 phase 3 trial are awaited.60

**Impact of Immunotherapy and Biomarker Testing on Quality of Life and Resource Utilization in NSCLC**

While NCCN guidelines recommend that all patients with advanced NSCLC be assessed for PD-L1 expression, this advice may not always be heeded and can lead to inadequate treatment initiation and possible increased cost as outlined below. Additional data discussed below show that immunotherapy use can help decrease costs related to admissions and improve health-related quality of life (QOL) through accurate biomarker testing. Pharmacists should concentrate on guideline- and evidence-based care when assessing and recommending biomarker testing and initiation of frontline treatment regimens.61

In an analysis of precision diagnostic testing (PDT) in NSCLC, among 37 identified studies and 64 defined scenarios, 11 scenarios compared PDT-guided therapy with non-guided therapy, 28 scenarios compared PDT-guided therapy with chemotherapy alone, and 25 scenarios compared PDT-guided therapy with chemotherapy alone with different PDT practices. Thirty-four scenarios (33%) were found to be cost-effective, 28 (44%) were found to not be cost-effective, 28 (44%) were found to not be cost-effective, and 2 were deemed as marginal based on the willingness-to-pay threshold within that country. All scenarios were cost-effective when PDT-guided therapy was compared with a therapy-for-all patient practice; however, only 7 of 37 studies had been designed to adequately confirm the cost-effectiveness of PDT-guided therapy. More approaches toward achieving PDT cost-effectiveness, value-based care, and positive outcomes in NSCLC should be completed.62

A retrospective study compared 3095 patients with advanced NSCLC receiving immunotherapy to a propensity-matched population of 3095 patients with NSCLC eligible for immunotherapy but who were treated with another regimen. Results found that PD-L1 testing was modest at 0.6 and 0.7 tests per patient in the immunotherapy versus non-immunotherapy groups, respectively. Higher total costs per patient occurred with advanced NSCLC receiving immunotherapy to a propensity-matched population of 3095 patients with NSCLC versus non-immunotherapy group (P = .029). While disease progression is known to negatively impact QOL regardless of treatment group, a lesser decline in QOL in those with progression is seen with pembrolizumab compared with chemotherapy; thus, refining and maintaining QOL measures is crucial at time of progression, as greater symptomatic burden and deterioration of QOL and psychological well-being can be seen.64,65

**TABLE 8. Maintenance Therapy Characteristics in Advanced NSCLC**

<table>
<thead>
<tr>
<th>Histology</th>
<th>PS</th>
<th>Continuation maintenance</th>
<th>Switch maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-squamous – EGFR</td>
<td>Bevacizumab (category 1)</td>
<td>Pemetrexed (category 1)</td>
<td>Pembrolizumab (category 1)</td>
</tr>
<tr>
<td>ALK, ROS1 mutation negative or unknown</td>
<td>Pembrolizumab (category 1)</td>
<td>Pembrolizumab (category 1)</td>
<td>Pembrolizumab (category 1)</td>
</tr>
<tr>
<td>SCC</td>
<td>Pembrolizumab (category 1)</td>
<td>Pembrolizumab (category 1)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Nivolumab (platinum-based)</td>
<td>Pembrolizumab (category 1)</td>
<td>Pembrolizumab (category 1)</td>
<td>Gemcitabine (category 2B)</td>
</tr>
<tr>
<td>Atezolizumab (category 1)</td>
<td>Pembrolizumab (category 1)</td>
<td>Pembrolizumab (category 1)</td>
<td>Gemcitabine (category 2B)</td>
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<tr>
<td>Pembrolizumab (category 1)</td>
<td>Pembrolizumab (category 1)</td>
<td>Pembrolizumab (category 1)</td>
<td>Gemcitabine (category 2B)</td>
</tr>
<tr>
<td>All histologies</td>
<td>3.4</td>
<td>Best supportive care</td>
<td></td>
</tr>
</tbody>
</table>

5S, performance score; SCC, squamous cell carcinoma.
6Pembrolizumab used with first-line platinum-based/platinum chemotherapy regimen.
7Pembrolizumab used with first-line platinum-based/platinum chemotherapy regimen.
8Pembrolizumab used with first-line platinum-based/platinum chemotherapy regimen.
9Pembrolizumab used with first-line platinum-based/platinum chemotherapy regimen.
10Pembrolizumab used with first-line platinum-based/platinum chemotherapy regimen.
11Pembrolizumab used with first-line platinum-based/platinum chemotherapy regimen.
12Pembrolizumab used with first-line platinum-based/platinum chemotherapy regimen.
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38Pembrolizumab used with first-line platinum-based/platinum chemotherapy regimen.
39Pembrolizumab used with first-line platinum-based/platinum chemotherapy regimen.
40Pembrolizumab used with first-line platinum-based/platinum chemotherapy regimen.
A meta-analysis assessing 2259 randomized controlled trials compared immunotherapy as monotherapy/in combination with chemotherapy or combined with another immunotherapy agent/targeted therapy with control groups not containing immunotherapy in patients with solid tumors. While the greatest benefit was seen with immunotherapy as monotherapy, results confirmed that immunotherapy can be added to other anticancer medications without causing a decline in QOL.68

While the introduction of immunotherapy agents has created a shift in the NSCLC treatment paradigm in terms of OS and QOL, these therapies are expensive and should be evaluated for cost-effectiveness.70

Nivolumab and ipilimumab combination treatment was found to have an increase in overall cost of $201,900 but also improved effectiveness of 0.50 quality-adjusted life-years (QALYs) when compared with chemotherapy, thus resulting in an incremental cost-effectiveness ratio of $401,700 per QALY. Of note, results did consider the cost and duration of therapy. Combination treatment was deemed cost-effective when treatment costs per month decreased from $26,425 to $5058 (80.9% reduction) or when immunotherapy use decreased from 24.0 months to 1.4 months in duration. Outcomes of a probabilistic sensitivity analysis determined that nivolumab-ipilimumab combination was less cost-effective compared with chemotherapy 99.9% of the time using a willingness-to-pay threshold of $100,000 per QALY despite trial results proving superior OS.71 Additionally, a 2016 study assessed the 1-year per-patient and worldwide costs associated with immunotherapy use for NSCLC. Based on the findings, pembrolizumab for NSCLC acquired 1-year per-patient costs of $130,511 while achieving a median PFS of 6.3 months. The 1-year worldwide cost for NSCLC treated with pembrolizumab was $83.9 billion.72 Another study assessed immunotherapy use in the United States from 2014 to 2019 and found that rates increased. The total Medicare spending on immunotherapies during this timeframe increased by 1916% from $285,506,498 to $5,755,319,571 while Medicare Part B drug spending increased by 57% from $23,679,547,748 to $37,271,080,631. Forty percent of the increase in overall Medicare Part B drug expenditure in this timeframe was due to immunotherapy, which corroborates unbalanced spending growth in the US government. One proposed solution to control spending growth is to tie payments to patient outcomes.73

The financial burden on patients is also exponential. Co-pay amounts may be untenable and patients may stay on immunotherapy for extended periods of time.74 Up to 40% of patients confirmed difficulty in paying medical bills, up to 11% reported missing treatments, with 12% opting for lower doses of prescription medicine, and 12% skipping other appointments or tests to ease overall costs.74 While costs may be waived for those participating in clinical trials, not all patients are candidates or wish to enter such trials.75 These factors, as well as missed work and lost income of families and caregivers, functions as further incentive to optimize treatment duration.74 Molecular predictive biomarkers can help determine which specific patients may benefit from these costly treatments. Tools such as cost-effectiveness, cost-benefit, QALY analyses, and various drug reimbursement modalities may also be valuable in reducing costs. Immunotherapies have succeeded in establishing long-term survival, but the rise in costs for cancer medications requires multidisciplinary collaboration and organization to preserve global health system use and access to patient care.76 Figure 2 summarizes current trends in immunotherapy-based challenges and offers possible mitigation strategies.

### Conclusion

Immunotherapies have drastically changed the treatment of advanced NSCLC in the past few years,
and management continues to advance swiftly as they become a cornerstone in the frontline setting. Oncology health care professionals require ample training and awareness regarding FDA-approved and developing immunotherapy-based metastatic NSCLC therapy approaches, as well as relevant clinical updates, barriers, and economic concerns in order to partake in optimal utilization among institutions and payers. Prioritizing guideline recommendations on biomarker testing and preferred treatments can positively impact QOL of patients while curbing clinical treatment pathways may be utilized in conducting ideal immunotherapy-based regimen selection.

REFERENCES


INSTRUCTIONS FOR RECEIVING CONTINUING PHARMACY EDUCATION (CPE) CREDIT

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1. Which statement is most accurate regarding biomarker testing assays for immunotherapy use in advanced non-small cell lung cancer (NSCLC)?
   A. Only 1 scoring system exists to identify the proportion of tumor cells expressing membranous staining at any level.
   B. Currently, assays are not interchangeable, and companion tests must be used with their corresponding companion immunotherapy agent.
   C. Programmed death-ligand 1 (PD-L1) immunohistochemistry 22C3 pharmDx assay is approved to identify patients eligible for ipilimumab and nivolumab use.
   D. Ventana PD-L1 (SP142) assay is approved to identify patients eligible for pembrolizumab.

2. An 83-year-old frail man with a history of hypertension and chronic obstructive pulmonary disease receives a new diagnosis of metastatic adenocarcinoma NSCLC. Biomarker testing reveals no actionable driver mutations but does reveal tumor proportion scoring (TPS) expression of 30%. What would be the most appropriate choice for an immunotherapy-based regimen for this patient?
   A. Atezolizumab + bevacizumab
   B. Cemiplimab
   C. Pembrolizumab
   D. Pembrolizumab + pemetrexed + carboplatin

3. Which of the following immunotherapy agents is approved as monotherapy for patients with PD-L1 expression ≥50% and also in combination with platinum-doublet chemotherapy for any histology of NSCLC?
   A. Cemiplimab
   B. Pembrolizumab
   C. Atezolizumab
   D. Ipilimumab

4. A 61-year-old male patient with a diagnosis of metastatic adenocarcinoma NSCLC with PD-L1 <1% recently completed 4 cycles of chemotherapy and immunotherapy with carboplatin, pemetrexed, and pembrolizumab. His recent imaging shows stable disease, and he is feeling well. What is the most appropriate choice for continuation maintenance for this patient?
   A. Best supportive care
   B. Carboplatin
   C. Atezolizumab
   D. Pembrolizumab + pemetrexed

5. Which of the following is true regarding the use of biomarker testing in NSCLC?
   A. Biomarker testing for PD-L1 expression has several challenges including lack of standardization of assays and heterogeneity of expression within a sample.
   B. PD-L1 expression is homogenous among tissue samples and is not impacted by disease therapy over time.
   C. Sequential biomarker testing has consistently proved to be more cost-effective than upfront next-generation sequencing (NGS) testing.
   D. US community-based oncology practices have high rates of biomarker testing for PD-L1 expression in patients with NSCLC.

6. If molecular testing is not possible, what is the most appropriate recommendation for treatment of advanced NSCLC?
   A. Patients should be treated as if they do not have any actionable driver oncogenes.
   B. Patients should receive immunotherapy as monotherapy.
   C. Patients should receive best supportive care.
   D. Patients should receive chemotherapy with a platinum agent.

7. In patients with metastatic NSCLC and PD-L1 expression levels greater than 30%, but who also have a targetable driver oncogene, such as EGFR L858R, what is the recommendation for treatment of advanced NSCLC?
   A. Patients should be treated as if they do not have any actionable driver oncogenes.
   B. Patients should receive first-line targeted therapy for EGFR L858R.
   C. Patients should receive immunotherapy as monotherapy.
   D. Patients should receive best supportive care.

8. Which scenario is a possible consequence of cytotoxic chemotherapy use if adequate biomarker testing is not completed for advanced NSCLC treatment?
   A. Decreased inpatient admissions and subsequent health care costs due to more manageable toxicity profiles
   B. Increased quality of life due to more favorable adverse effect (AE) profiles
   C. Decreased emergency department visits due to more favorable AE profiles
   D. Increased emergency department visits due to less favorable AE profiles

9. Which situation has been reported by patients/caregivers because of increased medical bills?
   A. Increasing time spent at work
   B. Decreasing quality of life
   C. Skipping appointments and treatments
   D. Increasing emergency department visits

10. Which scenario has been proposed to help curb costs of immunotherapy use in advanced NSCLC?
    A. Administer immunotherapies in the inpatient setting.
    B. Link payments to patient outcomes.
    C. Reduce biomarker testing to allow for standardized therapies among patients with NSCLC.
    D. Enroll more patients in clinical trials that waive costs.
NOW APPROVED

LIBTAYO in combination with platinum-based chemotherapy is indicated for the first-line treatment of adult patients with non–small cell lung cancer (NSCLC) with no EGFR, ALK or ROS1 aberrations and is locally advanced where patients are not candidates for surgical resection or definitive chemoradiation OR metastatic.

Approved in 2021:

LIBTAYO as a single agent is indicated for the first-line treatment of adult patients with NSCLC whose tumors have high PD-L1 expression (tumor proportion score [TPS] ≥50%) as determined by an FDA-approved test, with no EGFR, ALK, or ROS1 aberrations, and is locally advanced where patients are not candidates for surgical resection or definitive chemoradiation OR metastatic.

Visit LIBTAYOhcp.com for more information.

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.
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.

The incidence and severity of immune-mediated adverse reactions were similar when LIBTAYO was administered as a single agent or in combination with chemotherapy.

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 is more than 1 and up to 3 times ULN and 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. Thyroiditis led to withholding of LIBTAYO in 1.1% of patients. Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 83.3% 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.
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):
- **Nervous system:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, 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.
- **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

**LIBTAYO as a single agent:** The most common adverse reactions (≥15%) are musculoskeletal pain, fatigue, rash, and diarrhea.

**LIBTAYO in combination with platinum-based chemotherapy:** The most common adverse reactions (≥15%) are alopecia, musculoskeletal pain, nausea, fatigue, peripheral neuropathy, and decreased appetite.

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-1/L1, programmed death ligand-1; ROS1, c-ros oncogene 1 receptor tyrosine kinase.

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Immune-Mediated Pneumonitis (e.g., endocrinopathies and dermatologic reactions) are discussed below. Toxically managed adverse reactions that do not necessarily require systemic steroids adverse reactions are not controlled with corticosteroids.

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%) adverse reactions. Hepatitis led to permanent discontinuation of LIBTAYO in 0.1% of patients.

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.

Cardiac/Vascular:
Myocarditis, pericarditis, vasculitis

Endocrine:
Hypothyroidism, hyperthyroidism, adrenal insufficiency

LIBTAYO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow thyroiditis. Initiate hormone replacement or medical management of hypothyroidism as clinically indicated. Withhold LIBTAYO due to thyroiditis in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients.

Carcin/Vascular: Myocarditis, pericarditis, vasculitis

Neurological System: Meningitis, encephalitis, myasthenia gravis

Skin:
including all possible severe and fatal immune-mediated reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not be included in the table.

Other immune-mediated adverse reactions occurring in 1% (8/810) of patients receiving LIBTAYO include nephritis, hepatitis, and colitis. Severe or fatal cases have been reported for some of these adverse reactions.

Other Immune-Mediated Dermatologic Adverse Reactions
LIBTAYO can cause immune-mediated rash or dermatitis. The definition of immune-mediated dermatologic adverse reaction included the use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. In patients treated with other PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

Other immune-mediated adverse reactions as required to use systemic corticosteroids or other immunosuppressants and the absence of an alternate etiology. In patients treated with other PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

Other immune-mediated adverse reactions as required to use systemic corticosteroids or other immunosuppressants and the absence of an alternate etiology. In patients treated with other PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

Other immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including 3 (0.3%) and Grade 2 (0.4%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients.

Other Immune-Mediated Adverse Reactions
The following clinically significant immune-mediated adverse reactions occurred at an incidence of ≥ 1% in patients who received LIBTAYO or were treated with PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.
Adverse Reactions

The following serious 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)]
- Complications of Allogeneic HSCT [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

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

The 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 GC/SCG (Studies 1540 and 1423), 132 patients with advanced BCC (Study 1620), 355 patients with NSCLC (Study 1624), and 104 patients with other advanced solid tumors (Study 1423). LIBTAYO was administered intravenously at doses of 3 mg/kg every 2 weeks (n=265), 350 mg every 3 weeks (n=643), or other doses (n=32), 1 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, 200 mg every 2 weeks. Among the 810 patients, 57% were exposed for 6 months or longer and 25% were exposed for one year or longer. In this pooled safety population, the most common adverse reactions (≥25%) were musculoskeletal pain, fatigue, rash, and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥2%) were lymphopenia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia.

In addition, the data below reflect exposure to LIBTAYO in combination with platinum-based chemotherapy in 312 patients with NSCLC enrolled in a randomized, active-controlled trial (Study 16113).

6.2 Adverse Reactions in ≥10% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO and Chemotherapy in Study 16113

First-line treatment of NSCLC with LIBTAYO in Combination with Platinum-based Chemotherapy

The safety of LIBTAYO in combination with platinum-based chemotherapy was evaluated in 465 patients with locally advanced or metastatic NSCLC in Study 16113 [see Clinical Trials (14.3) in the full prescribing information]. Patients received LIBTAYO 350 mg every 3 weeks plus platinum chemotherapy every 3 weeks for 4 cycles (n=312), or placebo every 3 weeks plus platinum chemotherapy every 3 weeks for 4 cycles (n=153).

Adverse Reactions

Serious adverse reactions occurred in 25% of patients. The most frequent serious adverse reactions that occurred in ≥2% of patients were pneumonia, anemia, and neutropenia. Fatal adverse reactions occurred in 6% of patients who received LIBTAYO in combination with chemotherapy, including death not otherwise specified (2%), sudden death (1%), acute hepatitis (0.3%), acute respiratory distress syndrome (0.3%), meningitis: cerebral abscess (0.3%), pneumonitis (0.3%), and pulmonary hemorrhage (0.3%). LIBTAYO was permanently discontinued due to adverse reactions in 5% of patients. Adverse reactions resulting in permanent discontinuation in at least 2 patients were increased alanine aminotransferase and anemia.

Dosage interruptions of LIBTAYO due to an adverse reaction occurred in 33% of patients. Adverse reactions which required dosage interruptions in at least 2% of patients were anemia, pneumonia, neutropenia, thrombocytopenia, fatigue, COVID-19 infection, and pneumonia.

The most common (≥15%) adverse reactions were alopecia, musculoskeletal pain, nausea, fatigue, peripheral neuropathy, and decreased appetite. The most common Grade 3-4 laboratory abnormalities (≥2%) were anemia, neutropenia, thrombocytopenia, increased alanine aminotransferase, hypocalcemia, hyperkalemia, hypermagnesemia, and increased creatinine.

Table 6 summarizes the adverse reactions that occurred in ≥10% of patients and Table 7 summarizes Grade 3 or 4 laboratory abnormalities in patients receiving LIBTAYO and chemotherapy.

Toxicity graded per NCI CTCAE v.4.03

1. The denominator used to calculate the rate varied from 134 to 298 based on the number of patients with a baseline value and at least one post-treatment value.

First-line treatment of NSCLC with LIBTAYO as a single agent

The safety of LIBTAYO was evaluated in 395 patients with locally advanced or metastatic NSCLC in Study 1624 [see Clinical Trials (14.3) in the full prescribing information]. Patients received LIBTAYO 350 mg every 3 weeks (n=355) or investigator’s choice of chemotherapy (n=342), consisting of paclitaxel plus carboplatin or gemcitabine plus cisplatin or carboplatin; or paclitaxel plus carboplatin or gemcitabine plus cisplatin or carboplatin followed by optional pembrolizumab maintenance. The median duration of exposure was 27.3 weeks (9 days to 115 weeks) in the LIBTAYO group and 17.7 weeks (8 days to 86.7 weeks) in the chemotherapy group. In the LIBTAYO group, 54% of patients were exposed to LIBTAYO for ≥6 months and 22% were exposed for ≥12 months.

The safety population characteristics were: median age of 63 years (31 to 79 years), 44% of patients 65 or older, 88% male, 86% White, 82% had metastatic disease and 18% had locally advanced disease and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 (27%) and 1 (73%).

LIBTAYO was permanently discontinued due to adverse reactions in 8% of patients; adverse reactions resulting in permanent discontinuation in at least 2 patients were pneumonia, pneumonia, ischemic stroke and increased aspartate aminotransferase. Serious adverse reactions occurred in 28% of patients. The most frequent serious adverse reactions in at least 2% of patients were pneumonia and pneumonitis.

Table 7 summarizes the adverse reactions that occurred in ≥10% of patients and Table 8 summarizes Grade 3 or 4 laboratory abnormalities in patients receiving LIBTAYO.

Table 7: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥1% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO and Chemotherapy in Study 16113

Table 8: Adverse Reactions in ≥10% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1624

Table 9: Adverse Reactions in ≥10% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1624

The safety of LIBTAYO was evaluated in 395 patients with locally advanced or metastatic NSCLC in Study 1624 [see Clinical Trials (14.3) in the full prescribing information]. Patients received LIBTAYO 350 mg every 3 weeks (n=355) or investigator’s choice of chemotherapy (n=342), consisting of paclitaxel plus carboplatin or gemcitabine plus cisplatin or carboplatin; or paclitaxel plus carboplatin or gemcitabine plus cisplatin or carboplatin followed by optional pembrolizumab maintenance. The median duration of exposure was 27.3 weeks (9 days to 115 weeks) in the LIBTAYO group and 17.7 weeks (8 days to 86.7 weeks) in the chemotherapy group. In the LIBTAYO group, 54% of patients were exposed to LIBTAYO for ≥6 months and 22% were exposed for ≥12 months.

The safety population characteristics were: median age of 63 years (31 to 79 years), 44% of patients 65 or older, 88% male, 86% White, 82% had metastatic disease and 18% had locally advanced disease and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 (27%) and 1 (73%).

LIBTAYO was permanently discontinued due to adverse reactions in 8% of patients; adverse reactions resulting in permanent discontinuation in at least 2 patients were pneumonia, pneumonia, ischemic stroke and increased aspartate aminotransferase. Serious adverse reactions occurred in 28% of patients. The most frequent serious adverse reactions in at least 2% of patients were pneumonia and pneumonitis.

Table 7 summarizes the adverse reactions that occurred in ≥10% of patients and Table 8 summarizes Grade 3 or 4 laboratory abnormalities in patients receiving LIBTAYO.

Table 8: Adverse Reactions in ≥10% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1624

Table 9: Adverse Reactions in ≥10% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1624

The safety of LIBTAYO was evaluated in 395 patients with locally advanced or metastatic NSCLC in Study 1624 [see Clinical Trials (14.3) in the full prescribing information]. Patients received LIBTAYO 350 mg every 3 weeks (n=355) or investigator’s choice of chemotherapy (n=342), consisting of paclitaxel plus carboplatin or gemcitabine plus cisplatin or carboplatin; or paclitaxel plus carboplatin or gemcitabine plus cisplatin or carboplatin followed by optional pembrolizumab maintenance. The median duration of exposure was 27.3 weeks (9 days to 115 weeks) in the LIBTAYO group and 17.7 weeks (8 days to 86.7 weeks) in the chemotherapy group. In the LIBTAYO group, 54% of patients were exposed to LIBTAYO for ≥6 months and 22% were exposed for ≥12 months.

The safety population characteristics were: median age of 63 years (31 to 79 years), 44% of patients 65 or older, 88% male, 86% White, 82% had metastatic disease and 18% had locally advanced disease and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 (27%) and 1 (73%).

LIBTAYO was permanently discontinued due to adverse reactions in 8% of patients; adverse reactions resulting in permanent discontinuation in at least 2 patients were pneumonia, pneumonia, ischemic stroke and increased aspartate aminotransferase. Serious adverse reactions occurred in 28% of patients. The most frequent serious adverse reactions in at least 2% of patients were pneumonia and pneumonitis.
disorders or altering the normal immune response. 

Based on its mechanism of action, fetal exposure to cemiplimab-rwlc may increase the risk of developing immune-mediated disorders in these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

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-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 LIBTAYO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to cemiplimab-rwlc may increase the risk of developing immune-mediated disorders or altering the normal immune response. 

Table 9: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥1% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1824

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LIBTAYO N=355</th>
<th>Chemotherapy N=342</th>
<th>Grades 3-4&lt;sup&gt;a&lt;/sup&gt; %</th>
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</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Increased aspartate aminotransferase</td>
<td>3.9 1.2</td>
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<td></td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>2.7 0.3</td>
<td></td>
<td></td>
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<tr>
<td>Increased alkaline phosphatase</td>
<td>2.4 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased blood bilirubin</td>
<td>2.1 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>1.8 1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>1.2 1.6</td>
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<tr>
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<td>Lymphopenia</td>
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<tr>
<td>Anemia</td>
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<tr>
<td>Electrolytes</td>
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<tr>
<td>Hypercalcemia</td>
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<tr>
<td>Hypocalcemia</td>
<td>1.2 2.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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 lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death [see Data].

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

**Contraception**

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

LIBTAYO as a Single Agent

Of the 810 patients who received LIBTAYO as a single agent 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 mCSCC or laCSCC who received LIBTAYO as a single agent 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 BC who received LIBTAYO as a single agent 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.

LIBTAYO in combination with Platinum-based Chemotherapy

Of the 312 patients with NSCLC who received LIBTAYO in combination with platinum-based chemotherapy in Study 16113, 35% were 65 years up to 75 years and 6% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

12 CLINICAL PHARMACOLOGY

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of cemiplimab-rwlc or of other cemiplimab products.

During the treatment period ranging from 8 to 19 months in 5 clinical studies, the incidence of anti-cemiplimab-rwlc antibodies in LIBTAYO-treated patients was 2% (22/1029).

There was no identified clinically significant effect of anti-cemiplimab-rwlc antibodies on PK of LIBTAYO over the treatment duration ranging from 8 months to 19 months. Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the pharmacodynamics, safety, and/or effectiveness of LIBTAYO is unknown.

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CONTINUED FROM COVER

A longtime board member for Evidence-Based Oncology™ (EBO), Gamble spoke with EBO about his work with COA, his accomplishments, surprises, what he will miss, and some predictions for cancer care in the next 5 years. This interview has been edited for clarity.

**EBO:** What accomplishments during your time with COA are you most proud of?

**Gamble:** As far as specific accomplishments, I would probably name 3. One is the growth of our network for peer-to-peer support, the Administrators’ Network. I started that process back when COA was young—we were like just a year or two getting started—and I was at a practice. Ted [Okon, MBA, executive director of COA] and the team said that we really want to engage the administrators. We started a group of maybe 5 people back almost 20 years ago, and now we have close to 1000, so we’ve been growing that network. And we don’t have the magic sauce—we’re just the conduit that says “talk to each other,” and we’ll facilitate those discussions so people who are doing great things can share with people who are struggling, and vice versa, to help each other to just grow. It has been phenomenal to see the growth. We’ve had calls once a month, usually sharing best practices among people. That’s been one accomplishment.

The second one, I’d say, is just being involved in the reform space. As you know, in this world of health care, the more we know, sometimes the more we feel, “This doesn’t make any sense. We need to fix it.” There’s so much misalignment for patient care as it should be, and getting rid of obstacles so that care is for them. You see insurance premiums going up, coverage getting lower, obstacles all over the place [when you’re] trying to help the patients. In cancer care particularly, we’re seeing physicians leaving community practices and going to other sites of care, which is usually twice as expensive, and now we’re arguing if the quality is good. That shouldn’t happen; we should fix that. So, we’re trying to create some visibility and some education, [the point of which is to] say preserve and protect and promote high-quality, value-based care. We would argue, and we want to prove, that it’s on the community center. So, while we’ve made progress in that area, we’re not there yet… and the more we know, the more we know there is to do. So, we’re pondering—trying to find those issues, make them transparent and visible, and try to address them.

The third item is one that’s near and dear to my heart. I shared it last week at our payer summit, and that is a collaboration and partnership with ASCO for the new and improved OMH APC4 Program, which is ASCO’s patient-centered cancer care program.

We’ve challenged people and said, “Tell us what needs to be changed.” We cannot come up with a single payment model that works for everybody. There are too many other ideas, and even pride and egos, “mine is better than yours.” It would be a waste of breath if we tried to say [one solution works for all]. However, we are of the belief that we can come to an agreement on the specifics of what makes high-quality cancer care, specifically, for everybody—for the patient to look for, for insurance companies to look for, for employers, for providers, all moving in that direction—and then you can build anything you want to on top of it.

That’s what’s so magical about this program. To me, it’s the most meaningful, important thing that I’ve seen in cancer care in the time I’ve been in cancer care—which is now about 25 years. It just makes good sense, and it’s good for everybody. The standards are out there. You think you’re doing it? Hey, go for it, do it. When you’re ready for us to look behind you and see if you’re there, we’d be glad, but go ahead, move in these directions… Say I’m a patient coming in off the street, and I want the best cancer care. How do I know yours is best? You have to prove it to them.” That’s what makes this so good. I’m looking forward to the end of the pilot, which will be in June 2023, and hopefully we can start a national program [that will generate] lots and lots of interest.

We’ve got a standardized blueprint that we’ll continue to improve for all to follow for high-quality cancer care.

“We’re not anti-340B; we’re pro-patient. Therefore, if you’re getting assistance to help patients, help patients. Don’t help your profit center, your bottom line; that’s not what it’s about.”

—Bo Gamble, director, strategic practice initiatives, Community Oncology Alliance

**EBO:** What has surprised you over the years?

**Gamble:** One surprise that has really aggravated me [is that] COA has the reputation of being anti-340B. We are not anti-340B; we’re pro-patient. Therefore, if you’re getting assistance to help patients, help patients. Don’t help your profit center, your bottom line; that’s not what it’s about. I grew up in health care—good gracious—before I got involved in cancer care. I don’t know if you’ve ever heard of the Hill-Burton [Act and program], which started in 1946. It was a [federal government] program that said, we want hospitals to be able to do the capital improvements to make sure that they provide [good] care. And we’ll help you, we’ll give you some low-interest loans, whatever, to give you some ability to make that happen. In exchange, you have to help patients. You had to have patients apply for [benefits] and prove their income level, and based on their income level, they got either free care or greatly discounted care. Just wrote it off. It was for the patient.

Why can’t we get back to that? Because that was when health care prices were low, patients were getting access, they were getting care, there was no fear of going to the hospital because I’m going to bankrupt my family. It was about the patient. Why can’t we get back to that? That’s just so simple; it’s not that hard. We need to have assistance programs specifically for the patient. To me, if there was 1 thing, 1 thing that I think we could accomplish that would send a signal like, “Nope, we’re going to start doing things right,” it would be to fix that program. It’s just gotten crazy, it’s just gotten out of control, and for all the wrong reasons. That’s the one thing that surprised me. “
There were other [surprises, too, like the] ways certain guidelines are written—for instance, Medicare Advantage and how they’re allowed to have these obstacles in the way. Fix that, too. We need to get rid of all obstacles that are getting in the way of the patient getting their care. My argument is—and I think it’s universal to COA—that we believe that community cancer care provides the best quality, best value, and best care. Level the playing field, and may the best man win. And if we’re not the best, we’ll work hard to (become the best), but level the field so that we can play fairly all the way around, so there’s incentive to do the right thing and not an incentive to do [something] that’s just not healthy.

EBO: What’s next for Bo Gamble?

GAMBLE: Well, I’ve got 5 grandkids and I want to find time to see them and introduce myself to them. We’ve also got some new members of our staff—they are sharp young people, eager, bright minds. I’m motivated to support them so that they can carry these issues forward and do it better than we’ve ever done it before.

The other thing is that I’ll continue to work with ASCO, with a promotion of the OHM APC4 program, which to me is the most meaningful thing that we could do to help everybody involved in cancer care. Our challenge is that we need 10 of us to get out there and share it with the rest of the world, because this is so good. We feel that strongly about it. So, between all those [things], I’ll be somewhat busy. I want to be busy. It’s going to sound corny and clichéd, but we’re on this planet to serve. And I want to continue to serve and encourage as long as I live. So, even though I’ll be slowing down a little bit, I’ll go forward into next year with these young people [and] I’ll be there supporting them. As long as I’m adding value, I’ll stay around. If I’m not adding value, you tell me, and I’ll go fishing.

EBO: What will you miss?

GAMBLE: There is a reason they call it health care. I think [I’ll miss] seeing the quality and quantity of genuinely caring people who want to do good. And the contacts and relationships I’ve developed along the years, and seeing these heroes who think outside the box and say, “This is the right thing to do. This is what I’m going to do.” Being a part of that and watching it, it’s just been incredible, and I’ll miss that. I’ll stay in touch with some of that. But before I die, I’ll like to see cancer care, and maybe all health care, being reshaped into what it should be. Not what it is today. That’s my goal.

EBO: We’re going to do a lightning round. What are your 3 predictions for cancer care for the next 5 years?

GAMBLE: Number 1, I think that eventually we will address the 340B program. Hopefully, it will follow the patient—wherever the patient’s getting care, [the program] will provide the assistance.

Number 2, I think we’ll see some improvements on payment in a standardized way. Of course, the [Center for Medicare and Medicaid Innovation] is trying to do their thing, which is complicated—maybe some would argue a little overly complicated. You’ve got other people trying to keep up, just as we’re seeing standards developed in care with ASCO. I think we’ll see some standards in payment also, that reward [people] for doing the right thing.

Number 3, hopefully, you’ll see a radical change in the way insurance benefits are structured, so that benefits also aligned with getting the right thing done. I’ve shared this story before, and I’ll share it again. Working with OHM APC4 program, there is a standard that says if you are a cancer patient, you must be introduced to a concept that if you have end-stage cancer, you must have a discussion about what are your wishes before you die. It’s that simple: Ask the patient about where they want to be. We asked this question to all the pilot practices. And some said, “Yeah, we’re doing it.” And we were like, “OK, where is the proof of how well you’re doing it?” And that’s where they struggled.

So many arguments that we got back came down to, “Well, I want to [have the conversation], but the patient doesn’t want to pay for another office visit.” So, boom! Get rid of that patient out-of-pocket (expense).

That end-of-life discussion is so very important, not only from a quality standpoint, but from a value standpoint. Make it easy for the doctor and make it easy for the patients to do the right thing—to have that discussion. I’ve seen it play out in my family—close family, extended family—and that discussion is probably the most important discussion that will happen in their lifetime: “I’m dying from cancer, I want to go home,” or “I’m dying from cancer. I don’t want to be a burden to my family. I want to be in hospice,” or “I don’t want to have pain [even though I have] cancer.” Have those discussions, and then help those patients with their needs, [Instead, what we] sometimes do is treat patients until death, and that’s not healthy for the patient or the family. Start making it easy for the patient to do the right thing. I’d like to see that.

REFERENCE

AON to Become Public Company Through Business Combination Agreement

AMERICAN ONCOLOGY NETWORK (AON) announced October 6, 2022, that they have entered into a definitive business combination agreement with Digital Transformation Opportunities Corp. (DTOC) pursuant to which AON will become a public company (the “Business Combination”).

Upon the closing of the Business Combination, AON’s senior leadership team will continue to serve in their current roles. The combined company will be led by AON’s CEO Todd Schonherz, President and Chief Development Officer Brad Prechtl, Chief Financial Officer David Gould, and Chief Medical Officer Stephen “Fred” Divers, MD. AON’s existing board, which is composed of practicing medical oncologists, is expected to remain in place and will be joined by additional members affiliated with DTOC.

“This transaction represents the next step in AON’s journey to become the leading platform for community-based oncology practices. Since launching the AON platform in 2018, we’ve been able to drive consistently strong growth by providing our physician partners with a strong suite of practice management tools and ancillary services as well as access to the financial benefits associated with being integrated with a scaled platform,” Schonherz said in a statement. “We look forward to continuing to grow our network of physician partners and supporting them with our physician practice management platform.”

REFERENCE
Data Sharing From Cancer Drug Trials Falls Short of Promises, Study Authors Say

MARY CAFFREY

CONTINUED FROM COVER

Although the authors say data availability has improved, some meta-analyses are impossible because data for certain top-selling drugs are off limits. Their paper pointed specifically to nivolumab (Opdivo), pembrolizumab (Keytruda), and pomalidomide (Pomalyst). The audit found that 90% of the trial data for these 3 therapies were unavailable. The authors noted that this trio of therapies generated $30 billion in revenue in 2020.1

The top reasons given when trial sponsors were asked why IPD were ineligible for sharing was that the trial was ongoing (53%), or that the trial was complete but the IPD were still under embargo (21%). In their paper and during the EBO interview, Modi and Hopkins rejected these reasons, stating that, given the level of activity in cancer drug development, sharing anonymized IPD is essential for robust research on newer anticancer medicines.

“The concerning aspect of what we found in our study was that some of the most-used medicines—those having the most money spent on their use—were found to have the least transparency in the data,” Hopkins said. “It is a little bit concerning that when medicine seems to be a high-profit kind of medicine, it hasn’t been set up in a way to share that data.”

This fact is of concern to philanthropic groups that Hopkins works with because when drugs are new it may be too early for these entities to find real-world, postmarketing evidence to guide decision-making. But the greater concern with IPD sharing is that evidence be available for secondary analyses and to design new trials, he said.

Support for the audit came from author fellowships or grants from Cancer Council Australia and the National Health and Medical Research Foundation. Two coauthors on the audit reported unrelated research support from Pfizer.

Multiple Requests for Data Status

The audit stemmed from Hopkins’ 2018 research on data availability.3 Attempts to gain access were met with statements that IPD were ineligible for release, which Hopkins noted was in direct conflict with the companies’ stated policies.

Modi’s research involved the use of artificial intelligence in treating patients with breast cancer—another project that required requests for clinical trial data. “What we were getting in responses was, ‘These data are not eligible to share.’ And then we said, ‘Hold on, this doesn’t really match your data-sharing policies,’” he said.

In the interview, Modi described audit methods, which first required identifying all anticancer medicines approved by the FDA between January 1, 2011, and June 30, 2021. Using product labels accessed through the National Institutes of Health DailyMed database, the authors compiled a list of all clinical trials with results that were used in the approval process for the therapies. This resulted in a list of 304 trials for 115 different therapies. All trials were registered on ClinicalTrials.gov.

Trial start and completion dates were of interest because the authors noted those that started after January 1, 2014. This was the effective date of an agreement on transparency for IPD, which was developed jointly by industry trade groups, the Pharmaceutical Research and Manufacturers of America (PhRMA) and the European Federation of Pharmaceutical Industries and Associations (EFPIA).4 Of the 304 trials in the audit, the authors noted that 140 (46%) had a start date before January 1, 2014.

“Less than 3 years had passed since the results summary was added to the product label for 136 (45%) of the trials, 3 to 7 years for 126 (41%) trials, and more than 7 years for 42 (14%) trials,” the authors wrote.5

Among the companies involved, the authors found that 24 belong to 1 or both signatories to the 2014 transparency pledge, 19 have published an IPD policy on their website or a third-party source, and 21 lack a published IPD policy.

Modi then described the painstaking process of contacting all the trial sponsors to learn IPD eligibility. Of the 304 industry-sponsored trials in the audit, IPD sharing eligibility was publicly available for 64 trials (21%). For the remaining trials, Modi contacted the sponsor to determine the status. He created a cadence of reaching out every 30 days until he received a response. In some cases, the drug was no longer owned by the initial trial sponsor, which created delays. In the end, 9 trials (3%) sponsored by 8 different companies offered no response on the eligibility status of the trial data.

The contacts themselves were straightforward, Modi explained. “Our email is just asking them, ‘[Are these] data eligible to share or not? And if not, just give us a reason,’” he said. “The median response time was 42 days because they took their time until I followed up, then followed up again.”

Variation Among Companies

Amid some frustration, there was good news. The authors found the IPD were eligible for sharing from 136 trials, involving 60 anticancer drugs and data from more than 70,000 patients. Data were available from more than 50% of the trials for atezolizumab (Tecentriq), abiraterone (Zytiga), enzalutamide (Xandi), ibritinib (Imbruvica), osimertinib (Tagrisso), palbociclib (Ibrance), and pertuzumab (Perjeta).

“Furthermore, 5 of the top 20 pharmaceutical companies by revenue (Amgen, AstraZeneca, Boehringer Ingelheim, Pfizer, and Sanofi) indicated that more than 75% of their sampled oncology trials were eligible for IPD sharing,” the authors wrote. These achievements, they wrote, are a direct result of the 2014 data sharing principles “and are a beacon of hope to one of the least trusted industries in the world.”

In their paper and in the interview, the authors called on regulatory agencies and journal editors to take stronger stands in support of data sharing. Three specific recommendations are:

• Pharmaceutical sponsors should join PhMRA and/or EFPIA and establish a data sharing policy;
• Sponsors should establish an IPD sharing process external to the company, recognizing there may be conflicts of interest; and
• Enact a policy that states “all IPD underlying results presented in a product label will be immediately available for sharing.” This element is designed to remove extended embargo periods and ensure that registration of product triggers availability of clinical data.1

Hopkins said changes are needed to promote research to improve patient care. A major reason for requesting trial data, »
he said, is to allow systemic evaluation of data in search of signals related to race or sex. A second reason is to address variability in the quality of data provided, Hopkins said.

“Some companies put in a lot of care with the data that they provide. And they’re also transparent as to what data [were] collected throughout the entire trial—you can see that in the data dictionary,” Hopkins said. With other companies, “they don’t give the data dictionary and they redact a lot of the clinical data,” he said.

For investigators looking to study signals into differences in rates of AEs by race or sex, the way these data are reported matters a lot, he said. With the current emphasis on reducing disparities in cancer care, it would seem to matter more than ever how these data are shared. Today, some companies do a very good job in this area, Hopkins said, but others do not.

“So that’s the next step—trying to set standards around actual data provision,” he said.

REFERENCES

COMMENTARY

PBM Fees Put the “GER” in Danger for Specialty Pharmacies

DARRELL L. WILLYARD, PHARMD; AND ALEXIS V. FANSHIER, BA

CONTINUED FROM COVER

This article will discuss the real-world consequences of GER fees within specialty pharmacies, specifically oral oncology pharmacies. It is important to note that other pharmacies dispensing high-cost generics also may be affected.

Pharmacy benefit managers (PBMs) began as intermediaries between insurers and providers. In recent years, mergers and acquisitions have led to PBMs being under the same roof with insurers, specialty pharmacies, and, in some cases, provider services. Three PBMs (Express Scripts, CVS Caremark, and OptumRX) control approximately 89% of the market. All 3 PBMs also own specialty pharmacies, making it lucrative for them to keep prescriptions within the pharmacies they control.

PBMs and MIPs often struggle over which entity should provide pharmacy care for patients. MIPs are specialty pharmacies embedded in the patient’s medical clinic that offer several advantages over PBM-owned specialty pharmacies.1,4

PBMs may need assistance from providers to obtain necessary information when filling specialty prescriptions, which can delay patient care. MIPs have access to the patient’s chart, allowing them to easily retrieve needed information such as the appropriate International Classification of Diseases, Tenth Revision codes, allergies, past medical history, and patient demographics. The physician’s office is easily accessible to the MIP for collaboration and order clarification. Often, the patient may meet directly with the pharmacist for face-to-face education or to provide signatures for needed grants. MIPs are skilled at working with patients to obtain free drugs from the manufacturer when needed. This service is often not offered by other specialty pharmacies.

PBMs typically mandate that their commercially insured patients use the PBM’s specialty pharmacy.1,4 CMS oversees Medicare and allows patients to choose their specialty pharmacy. However, PBMs may prevent Medicare patients’ migration to other pharmacies through low-paying contracts or high DIR fees.1 Nebulous contracts and high DIR fees may keep MIPs from contracting with PBMs, which prevents the MIP from filling prescriptions for PBMs-insured patients.

Between 2010 and 2020, retroactive DIR fees increased by more than 100,000%.2 DIR fees are charged by PBMs outside of administration fees and are often collected after the point of sale (POS) and do not reflect the pharmacy’s actual reimbursement at the time of dispensing. Traditionally, DIR fees are based on so-called pharmacy performance metrics.2 DIRs have recoupment fees of up to 15% of the adjudicated price paid to the pharmacy for dispensing a prescription. PBMs develop and manage specific criteria used to score the contracted pharmacy.10

The scoring process varies from insurer to insurer and may include unachievable goals for specialty pharmacies focused on dispensing oncology medications. Unrealistic goals may include placing adherence ratings suitable for chronic diseases, such as type 2 diabetes or hyperlipidemia, on oral oncology drugs. Cancer drugs often require temporary discontinuation of treatment due to the adverse effect profile unique to that class of drugs and cancer disease state. For instance, pancytopenia is a common adverse drug reaction in many oral chemotherapy agents. In this example, the MIP prescriber may temporarily discontinue the patient’s oncology until their pancytopenia is resolved. However, PBMs may interpret this as nonadherence and increase DIR penalties.

Increasingly, PBMs contract with oncology practices. These fees are not based on pharmacy performance metrics but instead are calculated on a drug’s maximum allowable cost, wholesale acquisition cost, or average wholesale price (AWP).11 PBMs may...
contract with an entire network of pharmacies to pay a cumulative GER across generics dispensed by network pharmacies. GERs based on AWP may pay as low as AWP minus 85% to 89%. Although this may be appropriate for older, more competitive generic products, it does not work for all generics, including many cancer medications. AWP prices and the cost for generic drugs may be similar when the generic is first released but they tend to separate over time as the actual cost for older generic drugs continues to fall. Generic medications with actual costs exceeding 10% to 15% of their AWP will cause the pharmacy to lose money with this type of contract.

For example, a new generic version of sorafenib originally came to market with an AWP of more than $25,000 for a month's supply. The actual cost of the drug was as high as 60% of the AWP when it was first released. If a PBM pays the pharmacy at AWP minus 85%, the pharmacy could lose more than $11,000 each time the drug is dispensed (Figure).

In this example, the pharmacy would lose $11,250 each time this prescription was dispensed. Although dispensing the brand-name drug is an option and may remain profitable, the PBM may mandate the pharmacy to dispense the generic medication unless the prescriber or patient requests explicitly otherwise. Pharmacies losing money to GER fees may become more prevalent as more high-cost oncology drugs become generic.1

GER fees may occur at the POS or, more commonly, as a retroactive “take back” fee.10-13 Retroactive GER fees may remain hidden at POS, allowing the PBM to claw back money later as a single or multiple direct or indirect recoupment.

GER fees may be harmful to both patients and pharmacies. Patients may pay excessive co-payments if GER fees are adjudicated after POS. PBMs may take back thousands of dollars on a prescription that a patient has already purchased. The true-up potentially could have decreased the purchase price of the prescription, which would have also reduced the patient’s co-pay. In response, several states have enacted laws effectively eliminating post-POS GER fees.11 Additionally, CMS issued a final rule eliminating retroactive DDIR fees in Medicare Part D plans beginning in 2024. Although this will not eliminate DDIR or GER fees, this will move all DDIR fees to POS. By eliminating true-ups, pharmacies can effectively determine actual prescription payments to avoid financially toxic contracts. CMS also would benefit from the lower prescription price at POS.4

MIPs are embedded in oncology medical clinics, allowing for effective patient care in collaboration with various health care disciplines. MIPs have had to contend with growing DDIR fees shrinking the pharmacy’s profit margins for several years, but new GER fees potentially could deal the final blow to MIPs’ survival. MIP pharmacies could lose more than $10,000 per prescription when dispensing newly marketed high-cost generics. These fees may be hidden for an extended period, leading to financial devastation for smaller MIPs once discovered. Worst of all, these fees may make MIPs unable to contract with PBMs, forcing the pharmacy’s patients to rely on PBM-owned pharmacies and delay lifesaving oncology medications. New laws will prevent these hidden fees in the future, but will they come soon enough to save MIPs? The livelihood of MIPs, and in turn patient care, is of the essence.1

FIGURE. Example of Pharmacy Cost vs Pharmacy Payment

| R<sub>i</sub> | Cost | $25,000 | 60% | $15,000 |
| R<sub>e</sub> | Payment | $25,000 | 15% (AWP-85%) | $3,750 |
| Loss to pharmacy | | | | $11,250 |

The contractual agreement between PBM and PSAO can involve stipulations regarding DDIR fees potentially hidden in confusing language that could mislead the pharmacy’s understanding of reconciliations.10-13 This lack of transparency can be detrimental both to MIPs and their patients. It can drive specialty pharmacies to leave the contract with the PBM for financial reasons, pushing patients to go to cumbersome and less-accessible specialty pharmacies. Pharmacies discovering unreasonable GER fees should immediately contact their PSAO to discuss options for improved transparency. The pharmacy also could consider contacting the PBM about reasonable alternatives, such as addendums, which would exclude new generic drugs to market from the high GER rates.11

Generic effective rate (GER) fees may occur at the point of service (POS) or, more commonly, as a retroactive “take back” fee. Retroactive GER fees may remain hidden at POS, allowing the PBM to claw back money later as a single or multiple direct or indirect recoupment.
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