FEATURING: EUROPEAN HEMATOLOGY ASSOCIATION

POLICY

Health Insurance, Blood Cancer Care, and Outcomes: A Literature Review
Karen Crotty, PhD, MPH; Mariannna Lee, MSc; Katherine Breiman, PhD; Maria Sae-Hau, PhD; Candi Wines, MPH; Catherine Viator, MS; and Elisa Weiss, PhD

INTRODUCTION

The Patient Protection and Affordable Care Act (ACA) established several health insurance reforms important to cancer care in the United States, including prohibiting insurers from denying coverage or setting higher premiums on the basis of preexisting health conditions, expanding Medicaid eligibility to adults with incomes up to 138% of the federal poverty level, eliminating the Medicare Part D coverage gap or “donut hole,” and requiring commercial insurers to cover the cost of routine care that a patient receives while enrolled in a clinical trial. Yet despite these reforms, many patients with cancer continue to experience significant financial burden and distress associated with their care, referred to as the “financial toxicity” of cancer.3,4

Financial toxicity is particularly prevalent among patients with blood cancer, who are increasingly treated with expensive, orally administered anticancer drugs. A rapid rise in the cost of these drugs has offset the savings patients should have seen from the closing of the donut hole.5 Consequently, many of the more than 1.3 million people in the United States who are either living with, or are in remission from, blood cancer face higher out-of-pocket costs than patients with other cancers.6 Additionally, patients with blood cancer report a myriad of other access barriers, ranging from lack of insurance and inadequate provider networks to coverage denials. With recent growth in the availability of health plans that do not comply with the ACA’s market reforms, these barriers are likely to grow.7

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PAYMENT MODELS

Clinicians and Payers Expect to Wait and See Before Embracing CMS’ MIPS Value Pathways
Erin Crum, MPH

QUALITY MEASUREMENT

in federal health care programs has been around since at least 2007, when CMS introduced the Physician Quality Reporting System (PQRS) for providers caring for Medicare beneficiaries. The program continued to evolve, and it eventually became part of CMS’ Merit-Based Incentive System (MIPS), CMS’ first attempt to integrate several different incentive-based programs under one umbrella, including PQRS and meaningful use.8 The goal of MIPS is to optimize patient care by utilizing financial incentives to encourage providers to deliver high-quality, cost-efficient care.

CONTINUED ON SP245

PRACTICE TRANSFORMATION

ASCO, COA Release Updated Standards for Oncology Medical Home
Mary Caffrey

ON JULY 13, the American Society of Clinical Oncology (ASCO) and the Community Oncology Alliance (COA) released updated standards for the Oncology Medical Home (OMH), putting renewed emphasis on the importance of palliative care and ASCO’s Quality Oncology Practice Initiative (QOPI), which seeks to promote safety and best practices in the administration of chemotherapy.9 Details on the new standards were published in JCO Oncology Practice.10

A joint statement from the 2 groups stated that the new standards offers a roadmap for delivering “equitable, high-quality cancer care.”10

“In releasing the new standards, ASCO and COA seek to achieve a broad consensus among all stakeholders—including patients, clinicians, payers, purchasers, and employers—on what patients with cancer should expect and receive from their cancer care teams,” the groups said.

CONTINUED ON SP247

An illustration of hairy cell leukemia, a form of chronic lymphocytic leukemia, showing an accumulation of abnormal B lymphocytes.
FOR ADULT PATIENTS WITH MANTLE CELL LYMPHOMA (MCL)

BRUKINSA STAYS ON, SO BTK STAYS OFF

24-hour inhibition of BTK was maintained at 100% in PBMCs and 94% to 100% in lymph nodes when taken at the recommended total daily dose of 320 mg. The clinical significance of 100% inhibition has not been established.1,2

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage
Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematoma and hemotorax have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with BRUKINSA monotherapy. Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage. Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections
Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

Cytopenias
Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%) and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy.

Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

Second Primary Malignancies
Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

Cardiac Arrhythmias
Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Embryo-Fetal Toxicity
Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman.
BRUKINSA—THE BTK INHIBITOR DEMONSTRATED TO PROVIDE COMPLETE AND SUSTAINED INHIBITION1,2

**POWERFUL RESPONSES**

<table>
<thead>
<tr>
<th>STUDY 206</th>
<th>PET-BASED1</th>
<th>84% ORR (95% CI: 74, 91)</th>
<th>84% CR (95% CI: 74, 91)</th>
<th>19.5 mo MEDIAN DOR (95% CI: 16.6, NE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STUDY 003</td>
<td>CT-BASED1</td>
<td>84% ORR (95% CI: 67, 95)</td>
<td>22% CR</td>
<td>18.5 mo MEDIAN DOR (95% CI: 12.6, NE)</td>
</tr>
</tbody>
</table>

**DEMONSTRATED SAFETY PROFILE**

The most common adverse reactions (≥ 20%) included neutrophil count decreased, platelet count decreased, upper respiratory tract infection, white blood cell count decreased, hemoglobin decreased, rash, bruising, diarrhea, and cough.

The efficacy of BRUKINSA was IRC-assessed in 2 clinical trials that included a total of 118 adult patients with MCL who received at least one prior therapy. Tumor response was according to the 2014 Lugano classification for both studies, and the primary efficacy endpoint was ORR as assessed by an IRC. Study BGB-3111-206 (Study 206): N=86, Phase 2, open-label, multicenter, single-arm trial; PET scans were not required for response assessment. Study BGB-3111-AU-003 (Study 003): N=32, Phase 1/2, open-label, global, multicenter, single-arm trial; PET scans were not required for response assessment and the majority of patients were assessed by CT scan.

**INDICATION**

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

**ADVERSE REACTIONS**

The most common adverse reactions in > 10% of patients who received BRUKINSA were decreased neutrophil count (53%), decreased platelet count (39%), upper respiratory tract infection (38%), decreased white blood cell count (30%), decreased hemoglobin (29%), rash (25%), bruising (23%), diarrhea (20%), cough (20%), musculoskeletal pain (19%), pneumonia (18%), urinary tract infection (15%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for at least 1 week after the last dose. Advise men to avoid fathering a child during treatment and for at least 1 week after the last dose.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

**DRUG INTERACTIONS**

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

**CYP3A Inducers:** Avoid coadministration with moderate or strong CYP3A inducers.

**SPECIFIC POPULATIONS**

**Hepatic Impairment:** The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.
FOR BRUKINSA® (zanubrutinib)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematoma, and hematomas have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with BRUKINSA monotherapy.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

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

5.2 Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jirovecii pneumonia, and other infections according to the risk of infection in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

5.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (37%), thrombocytopenia (10%), and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy. Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

5.4 Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

5.5 Cardiac Arrhythmias

Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

5.6 Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for at least 1 week after the last dose. Advise men to avoid fathering a child during treatment and for at least 1 week after the last dose. This drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see Use in Specific Populations (8.1)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in more detail in other sections of the labeling:

• Hemorrhage [see Warnings and Precautions (5.1)]
• Infections [see Warnings and Precautions (5.2)]
• Cytopenias [see Warnings and Precautions (5.3)]
• Second Primary Malignancies [see Warnings and Precautions (5.4)]
• Cardiac Arrhythmias [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience

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

The data in the WARNINGS AND PRECAUTIONS reflect exposure to BRUKINSA as a single agent at 160 mg twice daily in 524 patients in clinical trials BGB-3111-AU-003, BGB-3111-205, BGB-3111-210, and BGB-3111-AU-002 and to BRUKINSA at 320 mg once daily in 105 patients in trials BGB-3111-AU-003 and BGB-3111-202. Among 829 patients receiving BRUKINSA, 79% were exposed for 6 months or longer and 61% were exposed for greater than one year. In this pooled safety population, the most common adverse reactions > 10% in patients who received BRUKINSA were neutrophil count decreased (53%), platelet count decreased (39%), upper respiratory tract infection (38%), white blood cell count decreased (30%), hemoglobin decreased (29%), rash (25%), bruising (23%), diaphoresis (20%), cough (20%), musculoskeletal pain (19%), pain (18%), urinary tract infection (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

Mantle Cell Lymphoma (MCL)

The safety of BRUKINSA was evaluated in 118 patients with MCL who received at least one prior therapy in two single-arm clinical trials, BGB-3111-206 [NCT03206970] and BGB-3111-AU-003 [NCT02434120] [see Clinical Studies (14)]. The median age of patients who received BRUKINSA in studies BGB-3111-206 and BGB-3111-AU-003 was 62 years (range: 34 to 86), 75% were male, 75% were Asian, 21% were White, and 94% had an ECOG performance status of 0 or 1. Patients had a median of 2 prior lines of therapy (range: 1 to 6). The BGB-3111-206 trial required a platelet count ≥ 75 x 10⁹/L and an absolute neutrophil count ≥ 1 x 10⁹/L, independent of growth factor support, hepatic enzymes ≤ 5 x upper limit of normal, total bilirubin ≤ 1.5 x ULN. The BGB-3111-AU-003 trial required a platelet count ≥ 50 x 10⁹/L and an absolute neutrophil count ≥ 1 x 10⁹/L, independent of growth factor support, hepatic enzymes ≤ 3 x upper limit of normal, total bilirubin ≤ 1.5 x ULN. Both trials required a CUR > 30 ml/min.

Both trials excluded patients with prior alloimmune hematopoietic stem cell transplant, exposure to a BTK inhibitor, known infection with HIV, and serologic evidence of active hepatitis B or hepatitis C infection and patients requiring strong CYP3A inhibitors or strong CYP3A inducers. Patients received BRUKINSA 160 mg twice daily or 320 mg once daily. Among patients receiving BRUKINSA, 79% were exposed for 6 months or longer and 68% were exposed for greater than one year. Fatal events within 30 days of the last dose of BRUKINSA occurred in 8 (7%) of 118 patients with MCL. Fatal cases included pneumonia in 2 patients and cerebral hemorrhage in one patient.

Serious adverse reactions were reported in 36 patients (31%). The most frequent serious adverse reactions that occurred were pneumonia (11%) and hemorrhage (5%). Of the 118 patients with MCL treated with BRUKINSA, 6 (5%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hepatitis B).

Table 3 summarizes the adverse reactions in BGB-3111-206 and BGB-3111-AU-003.

Table 4: Selected Laboratory Abnormalities (> 20%) in Patients with MCL in Studies BGB-3111-206 and BGB-3111-AU-003

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Percent of Patients (N=118)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood urea increased</td>
<td>29</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>ALT increased</td>
<td>28</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>24</td>
<td>0.9</td>
<td></td>
</tr>
</tbody>
</table>

*Based on laboratory measurements.
† Hyperuricemia and hypertension are known effects of BTK inhibition.

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia and Neutrophil count decreased</td>
<td>38 15</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia and Platelet count decreased</td>
<td>27 5</td>
</tr>
<tr>
<td></td>
<td>Leukopenia and White blood count decreased</td>
<td>25 5</td>
</tr>
<tr>
<td></td>
<td>Anemia and Hemoglobin decreased</td>
<td>14 8</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infection</td>
<td>39 0</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>15 10</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>11 0.8</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>36 0</td>
</tr>
<tr>
<td></td>
<td>Bruising</td>
<td>14 0</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal disorders</td>
<td>Diarrhea 23 0.8</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>13 0</td>
</tr>
<tr>
<td></td>
<td>Vascular disorders</td>
<td>Hypertension 12 3.4</td>
</tr>
<tr>
<td></td>
<td>Hemorrhage</td>
<td>11 3.4</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain 14 3.4</td>
</tr>
<tr>
<td></td>
<td>Respiratory, thymic and mediastinal disorders</td>
<td>Cough 12 0</td>
</tr>
</tbody>
</table>

* Includes all related terms containing bruise, bruising, contusion, ecchymosis
† Includes all related terms containing hemorrhage, hematoma
‡ Includes fatal adverse reaction
§ Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract infection viral
¶ Includes any related terms containing rash
# Includes any related terms containing hemorrhage, hematoma

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

- BGB-3111-206
- BGB-3111-AU-003
- NCT03206970
- NCT02434120
- BGB-3111-205
- BGB-3111-210
- BGB-3111-AU-002
- Grade 3 or higher
- Laboratory Parameter
- Percent of Patients
- All Grades (%)
- Grade 3 or 4 (%)
7 Drug Interactions

7.1 Effect of Other Drugs on BRUKINSA

Table 5: Drug Interactions that Affect Zanubrutinib

<table>
<thead>
<tr>
<th>Moderate and Strong CYP3A4 Inhibitors</th>
<th>Clinical Impact</th>
<th>Prevention or management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Co-administration with a moderate or strong CYP3A4 inhibitor increases zanubrutinib C&lt;sub&gt;max&lt;/sub&gt; and AUC [see Clinical Pharmacology (12.3)] which may increase the risk of BRUKINSA toxicities.</td>
<td>Reduce BRUKINSA dosage when co-administered with moderate or strong CYP3A4 inhibitors [see Dosage and Administration (2.3)].</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate and Strong CYP3A4 Inducers</th>
<th>Clinical Impact</th>
<th>Prevention or management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Co-administration with a moderate or strong CYP3A4 inducer decreases zanubrutinib C&lt;sub&gt;max&lt;/sub&gt; and AUC [see Clinical Pharmacology (12.3)] which may reduce BRUKINSA efficacy.</td>
<td>Avoid co-administration of BRUKINSA with moderate or strong CYP3A4 inducers [see Dosage and Administration (2.3)].</td>
</tr>
</tbody>
</table>

8 Use in Specific Populations

8.1 Pregnancy

Risk Summary

Based on findings in animals, BRUKINSA can cause fetal harm when administered to pregnant women. There are no available data on BRUKINSA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of zanubrutinib to pregnant rats during the period of organogenesis was associated with fetal heart malformation at approximately 5-fold human exposures (see Data). Women should be advised to avoid pregnancy while taking BRUKINSA. If BRUKINSA is used during pregnancy, or if the patient becomes pregnant while taking BRUKINSA, the patient should be apprised of the potential hazard to the fetus.

The estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Embryo-fetal development toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2- or 3-chambered hearts) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose of 160 mg twice daily.

Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 150 mg/kg is approximately 32 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a pre- and post-natal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g. cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5 times the AUC in patients receiving the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of zanubrutinib 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 from BRUKINSA in a breastfed child, advise lactating women not to breastfeed during treatment with BRUKINSA and for at least two weeks following the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BRUKINSA therapy.

Contraception

Females

BRUKINSA can cause embryo-fetal harm when administered to pregnant women [see Use in Specific Population (8.1)]. Advise female patients of reproductive potential to use effective contraception during treatment with BRUKINSA and for at least 1 week following the last dose of BRUKINSA, if this drug is used during pregnancy; or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

Advise men to avoid fathering a child while receiving BRUKINSA and for at least 1 week following the last dose of BRUKINSA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 641 patients in clinical studies with BRUKINSA, 49% were ≥ 65 years of age, while 16% were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between younger and older patients.

8.6 Renal Impairment

No dosage modification is recommended in patients with mild to moderate renal impairment (CLcr ≥ 30 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients with severe renal impairment (CLcr < 30 mL/min) or on dialysis [see Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment [see Dosage and Administration (2.2)]. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic impairment. Monitor for BRUKINSA adverse reactions in patients with hepatic impairment [see Clinical Pharmacology (12.3)].
FROM THE CHAIRMAN

Advances in Blood Cancers Come With Financial Toxicity

TWENTY YEARS AGO, the FDA approved imatinib (Gleevec), the tyrosine kinase inhibitor that converted the deadly chronic myeloid leukemia to manageable disease. More than a decade later, the pills that some called “magic bullets” were making news for a different reason. Leading physicians, including some scientists who ran the clinical trials that proved imatinib’s effectiveness, were signing letters to protest its cost.1 After first coming to market with a price of about $26,000, the drug’s cost kept rising year after year, until it reached $148,000 per year in 2015. Both physicians and patient advocates sounded the alarm: some patients with cancer were not staying on their medication or were skipping doses, not because of adverse effects, but because they couldn’t afford the life-saving drugs. The term “financial toxicity” began to appear in the literature, and by 2016 the price of prescription drugs had reached the political arena.2

Five years later, a review article appearing in this issue of Evidence-Based Oncology™ finds not much has changed for patients with blood cancers. Despite the promise of the Affordable Care Act (ACA), the 1.3 million Americans who are living with or are in remission from a blood cancer face higher out-of-pocket costs than patients with other types of cancer. The authors found these patients may experience coverage denials and inadequate provider networks; more recently, the return of health plans that do not comply with ACA’s market reforms has created additional barriers.

The coverage woes are frustrating in light of the advances in treating blood cancers. This issue includes coverage from the recent meeting of the European Hematology Association, which featured positive news about zanubrutinib (Brukinsa), the second-generation Bruton tyrosine kinase that is approved in mantle cell lymphoma and is being studied in other blood cancers. And, the authors conclude, the current body of evidence shows that insurance status and the patient’s type of insurance can impact survival, although more studies are needed to learn how insurance status affects clinical trial participation, quality of care, and quality of life.

The work funded by the Leukemia and Lymphoma Society calls for more research in these areas, as well as the effect of insurance status on vulnerable populations. If patients are not connecting to life-saving therapies, it is important to understand why.

Sincerely,
Mike Hennessy Sr
Chairman and Founder
MH Life Sciences™

REFERENCES
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Investigators Report Survival, Cost-effectiveness Data for Zanubrutinib
The Role of CAR NK Cells: Competition or Complement to CAR T-Cell Therapy?
Celltrion Releases First Real-World Data for Its Rituximab Biosimilar in DBLCI

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Todd Schlesinger, MD, FAAD: Surgical Decisions for Skin Cancer Are Multimodal
Ivo Abraham, PhD, RN, on How Neulasta Onpro Is Having an Impact on the Biosimilars Space
Sonia T. Oskouei, PharmD, BCMAS, DPLA, Differentiates Pharmacist Concerns From Physicians’ Regarding Biosimilars

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I have heard the word “value” bandied about in legislation, CMS demonstration project, or “shiny面上 they most. There is no single program, piece of available to the patients and families that need face in making the full breadth of cancer innovation fixes or magical remedies for the challenges that we these treatments actually receive them.

we struggle to create the requisite care networks and receptor T-cells, portend the ability to eff ectively advanced technology, such as chimeric antigen to struggle to create a sustainable model of how innovative, life-altering therapeutics, we continue tion. As we embrace a transformational pipeline of Aff ordable Care Act promised to change so much, on ossifi ed systems of care.

be beholden to seemingly intransigent barriers based well past the limitations of prior decades, we remain to systems that lack the plasticity to grapple with experience, and more sustainable care costs. I do

It is easy to become deluded that there are simple fixes or magical remedies for the challenges that we face in making the full breadth of cancer innovation available to the patients and families that need them most. There is no single program, piece of legislation, CMS demonstration project, or “shiny new object” that will cure the ills of our system. I have heard the word “value” bandied about in careless ways that distracts from the hard work and intradisciplinary collaboration that will be essential to fully define and subsequently realize a value-centered system of cancer care.

In this issue of Evidence-Based Oncology™, we see both the future of what can be, and the prosaic bumps in the road that will make a full realization of that future difficult. Mary Caff ey provides a summary of a recent webinar, “Genomic Testing Creates Opportunities for Collaboration Between Academic Centers, Private Sector.” This conversation covered potential steps in fostering and advancing more eff ective cancer care that is built upon the foundations of genomic testing and precision medicine delivery. We also examine what a more effective ecosystem for delivering care to cancer patients might look like in our review of the updated standards for an Oncology Medical Home between the Community Oncology Alliance and the American Society of Clinical Oncology. At the same time, the limits of our current system, including limitations in coverage for the cancer patients with blood cancers and our continued struggle with the creation of meaningful, actionable metrics for assessing oncology physician performance remind us of the ways in which our system struggles to adapt to this period of hyperdynamic change.

I remain an optimist that the lives of cancer patients and their families will continue to evolve in ways that will bring better outcomes, better patient experience, and more sustainable care costs. I do not, however, underestimate the extraordinary amount of work, collaboration, blood, toil, tears and sweat that it will take to get us there. Wherever we are, we will be there as a community of the experience, and more sustainable care costs. I do

We are, we will be there as a community of the experience, and more sustainable care costs. I do
WHEN HER2+ MBC PROGRESSES

PURSUE UNPRECEDEDENT SURVIVAL

TUKYSA + trastuzumab + capecitabine vs placebo + trastuzumab + capecitabine

Reduced risk of disease progression or death by 46%

Median PFS: 7.8 months (95% CI: 7.5-9.6) vs 5.6 months (95% CI: 4.2-7.1); HR = 0.66 (95% CI: 0.50-0.87); P < 0.0001

Extended median OS by 4.5 months

Median OS: 21.9 months (95% CI: 18.3-31.0) vs 17.4 months (95% CI: 13.6-19.9); HR = 0.54 (95% CI: 0.42-0.71); P = 0.0048

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

TUKYSAhcp.com

Indication

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

Select Safety Information

Warnings and Precautions

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

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

Please see full Important Safety Information on the following pages.

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

In combination with trastuzumab + capecitabine

TUKYSA extended overall survival*†

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

Important Safety Information

Warnings and Precautions

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

- **Hepatotoxicity:** TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5 × ULN, 8% had an AST increase >5 × ULN, and 1.5% had a bilirubin increase >3 × ULN (Grade ≥3). Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA discontinuation in 1% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

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

Adverse Reactions

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

**TUKYSA reduced the risk of disease progression or death**

**PRIMARY ENDPOINT**

**PFS**

46% reduction in the risk of disease progression or death†

- HR = 0.54 (95% CI: 0.42–0.71); P < 0.00001
- Median PFS: 7.8 months (95% CI: 7.5–9.6) in the TUKYSA arm vs 5.8 months (95% CI: 4.2–7.1) in the control arm

**EXPLORATORY ANALYSIS**††

**PFS AT 12 MONTHS**

<table>
<thead>
<tr>
<th>TUKYSA ARM</th>
<th>CONTROL ARM</th>
</tr>
</thead>
<tbody>
<tr>
<td>33% (33.1%; 95% CI: 26.6–39.7)</td>
<td>12% (12.3%; 95% CI: 6.0–20.9)</td>
</tr>
</tbody>
</table>

*Study design: HER2CLIMB was a randomized (2:1), double-blind, placebo-controlled trial of 612 patients with HER2+ MBC who received TUKYSA + trastuzumab + capecitabine (TUKYSA arm; n = 410) or placebo + trastuzumab + capecitabine (control arm; n = 202). Primary endpoint was PFS (time from randomization to documented disease progression or death from any cause) in the first 480 randomized patients. Secondary endpoints assessed in all randomized patients included OS (time from randomization to death from any cause), PFS was evaluated in accordance with RECIST criteria, version 1.1, by means of BICR.†† This exploratory analysis is descriptive only. These are estimates and not exact numbers. HER2CLIMB was not powered to assess a statistical difference between treatment groups at this time point.

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

**Lab Abnormalities**

In HER2CLIMB, Grade ≥3 laboratory abnormalities reported in ≥5% of patients who received TUKYSA were decreased phosphate, increased ALT, decreased potassium, and increased AST.

The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

**Drug Interactions**

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

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

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

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

**Use in Specific Populations**

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

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

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

Please see Brief Summary of Prescribing Information on adjacent pages.

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

### Dosage Modifications for Adverse Reactions

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

#### Table 1: Recommended TUKYSA Dose Reductions for Adverse Reactions

<table>
<thead>
<tr>
<th>Severity</th>
<th>Recommended TUKYSA Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea1</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td>Grade 3 or Grade 4</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
<tr>
<td>Grade 3 rash</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td>Grade 4 rash</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
<tr>
<td>Other adverse reactions1</td>
<td>Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td>Permanently discontinue TUKYSA.</td>
<td></td>
</tr>
</tbody>
</table>

1. Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03

### WARNINGS AND PRECAUTIONS

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

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

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

### ADVERSE REACTIONS

#### Clinical Trials Experience

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

**HER2-Positive Metastatic Breast Cancer (HER2CLIMB)**

The safety of TUKYSA in combination with trastuzumab and capecitabine was evaluated in HER2CLIMB. Patients received either TUKYSA 300 mg twice daily plus trastuzumab and capecitabine (n=404) or placebo plus trastuzumab and capecitabine (n=197). The median duration of treatment was 5.8 months (range: 3 days, 2.9 years) for the TUKYSA arm.

Serious adverse reactions occurred in 26% of patients who received TUKYSA. Serious adverse reactions in ≥ 2% of patients who received TUKYSA were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions leading to treatment discontinuation occurred in 6% of patients who received TUKYSA. Adverse reactions leading to treatment discontinuation of TUKYSA in ≥ 1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions leading to dose reduction occurred in 21% of patients who received TUKYSA. Adverse reactions leading to dose reduction of TUKYSA in ≥ 2% of patients were hepatotoxicity (8%) and diarrhea (6%).

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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA + Trastuzumab + Capecitabine (N = 404)</th>
<th>Placebo + Trastuzumab + Capecitabine (N = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81</td>
<td>12</td>
</tr>
<tr>
<td>Nausea</td>
<td>58</td>
<td>3.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Stomatitis2</td>
<td>32</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-planter erythrodysesthesia syndrome</td>
<td>63</td>
<td>13</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatotoxicity4</td>
<td>42</td>
<td>9</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25</td>
<td>0.5</td>
</tr>
</tbody>
</table>

1. Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03
2. Abbreviations: ULN = upper limit of normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase
3. Difference Between Arms of ≥5% Compared to Placebo in HER2CLIMB
4. P-glycoprotein (P-gp) Substrates:

   - TUKYSA and its logo, and Seagen and are US registered trademarks of Seagen Inc.
When given in combination with TUKYSA, the recommended dosage of capecitabine can be taken at the same time. Refer to the Full Prescribing Information for information about dosage modifications for these drugs.

### Dosage Modifications for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA + Trastuzumab + Capecitabine</th>
<th>Placebo + Trastuzumab + Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades ≥ 3 (%)</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>59</td>
<td>3.3</td>
</tr>
<tr>
<td>Decreased bilirubin</td>
<td>47</td>
<td>1.3</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>46</td>
<td>28</td>
</tr>
<tr>
<td>Increased AST</td>
<td>43</td>
<td>26</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>40</td>
<td>0.8</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Increased sodium</td>
<td>28</td>
<td>2.5</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>26</td>
<td>0.5</td>
</tr>
</tbody>
</table>

1. The denominator used to calculate the rate varied from 351 to 400 in the TUKYSA arm and 173 to 197 in the control arm based on the number of patients with a baseline value and at least one post-treatment value. Grading was based on NCI-CTCAE v.4.03 for laboratory abnormalities, except for increased creatinine which only includes patients with a creatinine increase based on the upper limit of normal definition for grade 1 (NO CTCAE v5.o).
2. Laboratory criteria for Grade 1 is identical to laboratory criteria for Grade 2.
3. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function.
4. There is no definition for Grade 2 in STCAE v4.03.

**Increased Creatinin:** The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

### Drug Interactions

**Effects of Other Drugs on TUKYSA**

**Strong CYP3A4 Inducers or Moderate CYP2C8 Inducers:** Concomitant use of TUKYSA with a strong CYP3A4 or moderate CYP2C8 inducer decreased tucatinib plasma concentrations, which may reduce TUKYSA activity. Avoid concomitant use of TUKYSA with a strong CYP3A4 inducer or a moderate CYP2C8 inducer.

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

**Effects of TUKYSA on Other Drugs**

**CYP3A Substrates:** Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates, where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.

**P-glycoprotein (P-gp) Substrates:** Concomitant use of TUKYSA with a P-gp substrate increased the plasma concentrations of P-gp substrate, which may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

### USE IN SPECIFIC POPULATIONS

**Pregnancy**

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

**Lactation**

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

**Females and Males of Reproductive Potential**

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

- Females: Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.
- Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.

**Infertility:** Based on findings from animal studies, TUKYSA may impair male and female fertility.

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

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

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

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

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Genomic Testing Creates Opportunities for Collaboration Between Academic Centers, Private Sector

MARY CAFFREY

IN RECENT YEARS, genomic testing has changed the face of cancer care, as it helps ensure more informed decision-making between doctor and patient in cancer care. But precision medicine solutions cannot be delivered equitably if some patients lack access to testing, or if tests results are used incorrectly.

A June 2, 2021, webinar from Oncology Value Coalition, a series presented by The American Journal of Managed Care® (AJMC®), featured experts from City of Hope National Medical Center, of Duarte, California, and AccessHope LLC, which delivers cancer care to employers and their health care partners. The panel also featured a representative from Highmark Blue Cross Blue Shield, the integrated delivery network based in Pittsburgh, Pennsylvania.

Serving as moderator was Joseph Alvarnas, MD, vice president for government affairs and chief clinical adviser for AccessHope. Alvarnas is also a clinical professor in the Department of Hematology & Hematopoietic Cell Transplantation at City of Hope and editor-in-chief of AJMC®’s Evidence-Based Oncology®. Joining Alvarnas were:

- Afaneh Barzi, MD, PhD; medical director, gastrointestinal oncology, AccessHope; director, employer strategy, associate clinical professor, Department of Medical Oncology and Therapeutics Research, City of Hope
- Sameera Rahman, MD; senior medical director, Highmark Inc
- Howard (Jack) West, MD; executive medical director, AccessHope; associate clinical professor, Department of Medical Oncology and Therapeutics Research, City of Hope

The Rise of Precision Medicine

Alvarnas explained that in the early 1950s and 1960s, cancer investigators “finally appreciated that cancer could, in fact, carry nonrandom genetic mutations.” The breakthrough discovery was the Philadelphia chromosome; at first, a broken chromosome was seen as a way to confirm diagnosis, but soon came the knowledge that the mutations were therapeutic targets that could change the course of treatment. ¹ Chronic myeloid leukemia was the first huge success story; in the past, patients faced a median survival of 3 years, and only 20% had an allogenic donor for stem cell transplantation. The arrival of tyrosine kinase inhibitors, specifically imatinib (Gleevec), turned chronic myeloid leukemia into a chronic disease.

“We now move to a future where a vast majority of patients do very well, simply taking a pill a day,” Alvarnas said. “What we previously referred to as magic bullets become a new reality. And when we look at other diseases, the application of genomic testing and more effective therapeutic risk stratification and alignment of therapeutics has profoundly changed cancer prognosis.”

The American Cancer Society has seen the biggest drops in cancer mortality in the past 2 years. ² “To think about it another way, there’s a life dividend that’s coming about as a result of more people surviving cancer,” Alvarnas said.

At the same time, the price of genomic testing has dropped, allowing testing to become more accessible, he said. “So, this conversation regarding precision medicine isn’t just an abstract one.”

Each panelist offered a brief introduction, with West explaining that as a thoracic oncologist, he’s seen the shift as investigators saw how EGFR mutations “really trumped clinical factors and were far more important. That was a sea change. And over the last decade or so, we’ve added greatly beyond EGFR to about 9 or so total mutations.” The field shifts every 6 to 12 months, as new market and targeted therapy joins the arsenal, offering fewer adverse effects.

“Now we have the challenge of all of these great markers, but they’re only valuable if you find them, or if you’re looking for them,” West said. “And I think that’s one of the biggest challenges we face.”

What Cancers Are Affected by Genomic Testing?

Alvarnas then asked the group to discuss where genomic testing had made the biggest mark. West said lung cancer has seen major treatment changes due to testing, but it’s not across the board. While he still sees many smokers who have a driver mutations, the bigger impact has been among patients with “nonsquamous [disease], especially adenocarcinomas,” including patients who never smoked. These patients are likely to be younger, with cancers that are less likely to be associated with the cumulative effects of a lifetime of damage.

“Beyond lung cancer, West said, genomic testing applies to many cancers, “especially those where there is not a clear environmental component, and it seems to be a random genetic event.” The ability to generate large increases in survival, “with lock and key” therapeutic regimens that can target exactly the right patients, means that those who are a good match will find their way to the trial, West said, even if travel is required. “It changes the value equation for potential candidates for these trials, And it makes it possible for us to do trials in these narrower populations.”

Barzi said she has always been “fascinated” that many discoveries have occurred by accident, including many treatments that were retrospectively discovered to only benefit that patients with EGFR mutations. “It allows us to recognize that the population of cancer we have is very heterogeneous,” she said. “And biomarkers are perhaps the only way to bring homogeneous populations together, to identify their values and give them treatment.”

What’s clear from basket trials that are not histology specific, she said, is that changing trial designs has allowed opportunities for patients with rare cancers to gain access to trials. That said, Barzi noted that factors in the tumor microenvironment mean “that having the same genomic alteration may not result in the same benefit,” with breast cancer drug development offering a strong example.

“We need to look at the biomarkers we need to find homogeneous populations,” Barzi said. “And the next question is, well, how do we test for biomarkers in a uniform way? And that brings us to what testing we should use?”

According to National Institutes of Health data, she said, “the number of diseases that can have genetic testing is rising exponentially,” and the same goes for the number of testing companies and the number of tests themselves. It can be confusing for the local provider who does not see many patients with a given type of cancer, especially when it comes to interpreting results.

“We have come to the age that we have a revolution in realizing the value of genomic and precision medicine. We changed how we design trials. But to make it happen in the population,” Barzi said, “we’ve got to think about the infrastructure of care delivery, which is our providers and our payers. How do we do that?”
The Payer Perspective
Alvarnas then turned to Rahman, asking how payers and employers can gain from the scientific advances—and how do they navigate all the incoming evidence?

"The complexity of care seems to increase over time," Rahman said. "At the same time, we have a lot of data sets that are eligible for this type of testing. Now, from a payer perspective, I can say that we are always very passionate about making sure that we're embracing evidence-based care based on guidelines, how we're always creating evidence-based medical policies and putting in evidence-based care models."

Patients, she said, don't understand how pathways work and rely on decisions by physicians for what treatments offer the best value. Payers want to understand what tests will offer that value, and how they can leverage data developed during clinical trials to gain insights. Highmark is using a clinician-led task force to design and develop its own medical policies and oncology care models, "so that we can provide the most clinically effective and highly quality care that's aligned with the evolution of the space."

The Changing Therapeutic Pipeline
Barzi said that the arrival of chimeric antigen receptor (CAR) T-cell therapy has been a game-changer, given the requirements for T-cell collection and a customized engineering process. "It is not a drug that can be given with a schedule—it requires an infrastructure," she said. This is not something that existing in CMS' Oncology Care Model in the community oncology practice—and these practices could not deliver CAR T-cell therapy when it was first developed.

West said the same was true of running clinical trials. Decades ago, drug trials were conducted in "a completely unsselected population, and got pretty poor results most of the time, even when we had successes."

Enter targeted therapies, and suddenly the math makes trials more cost effective. West, said, because it no means treating 100 patients to see 10 successes. Using checkpoint inhibitors for patients who have high PD-L1, but for those with low PD-L1, for example, means response rates will be much higher. Newer agents being used in a targeted manner are seeing response rates of 50% to 60%, whereas if they were used indiscriminately as in prior years, the response rates would be closer to 10%.

"But it is all predicated on getting detailed molecular testing, so that we can only ask questions today, but have the have the data to look back retrospectively and start asking the smartest questions for things we don't understand today," West said. "As we aggregate enough data, we can figure out why certain patients with this mutation responded to a targeted therapy, but others don't."

While this is good news, it presents challenges. Alvarnas noted that with the number of therapies reaching the market, and the number in the pipeline, the process of connecting patients with the therapy that matches their cancer takes time that many do not have. "So we have to grapple with the complexity of that in order to ensure that this pipeline finds its ability to get into the right people at the right time at the right place without unnecessary delays?"

Highmark’s Rahman said this is where a shift from traditional "utilization management" is needed. When it comes to innovation like CAR T-cell therapy, accessibility is a big issue, and health plans will need to work with physicians as "health care delivery partners," to make sure that patients get the care they need without adding new administrative burdens.

To achieve this, she said, "We have made sure that the health care delivery partners that we work with very closely have implemented certain care models in place." When it comes to a treatment such as CAR T-cell therapy, "it's not just the complexity in terms of like the services being rendered that adds to the member experience. But we're also looking at the physician experience, and we're thinking about what are some normal types of reimbursement methodologies that we can put into place, so that the provider experience can be improved.

"I think there's more to come in the next 5 years," Rahman said.

Barzi said this is where partnerships like AccessHope can make a difference. With AccessHope—which now includes City of Hope, Northwestern, and most recently, Dana-Farber Cancer Institute—there's real-time decision support for oncologists that offers reassurance for patients, providers, and payers. "It's an excellent solution to not only help the patients get the right thing, but help the oncologist be reassured that they are giving the right thing."

Ensuring Access to the Best Care
Alvarnas then turned to one of the most challenging topics in cancer care today: the fact that scientific advances are not reaching everyone. He referenced a report from the American Association of Cancer Research that found significant disparities in care by race, socioeconomic status, and geography. Even in wealthy states such as California, the divide exists.

One study, he said, "showed less than half of cancer patients in the state got [National Comprehensive Cancer Network] guideline concordant therapy, and an independent risk factor for not getting concordant care was being a beneficiary of the state Medicaid program."

AccessHope was created to address the issue of giving people in all parts of the country access to subspecialist care regardless of where they live. As West explained, serves are offered, "largely as an employee benefit" and the number of companies participating has grown steadily.

With the release of providers taking on more risk—and employers seeking the benefits of risk-based contracting, it's a concept that makes sense when the price of making the wrong decision could be very large. "For complex cases, with potentially high impact based on just on the risk of the cost of the therapies, the risk of the magnitude of difference between treatments that might be done in the best treatments that could be done," West explained.

"And, and so using this automated trigger list can help identify patients most likely to benefit from having a subspecialist review the case records and offer thoughts to the local team, and work in concert with the local oncologist to determine the best care where the patient is."

In most cases, patients don't have to travel to get treatments; AccessHope can work with the local oncology team. "This also includes discussion of potentially attractive clinical trials that could be available in that clinical setting and potentially in that area," West said.

With the pandemic, the ability to not travel for the best care has been attractive. Moving forward, West said, "It's going to be very appealing to work with payers so that it's not all based on employee benefits, but can be more broadly available to many, many patients and in different geographies."

Alvarnas noted that this concept fundamentally changes the traditional relationship between community oncologists and the academic centers. The use of telehealth during the pandemic opened everyone's eyes to the opportunities that were available, Barzi said, especially as a partner with the local provider.

"We have come to the realization that virtual care when the doctor is not in direct contact with the patient, could potentially be as good for many conditions, we really don't need to see or touch our patients to deliver the care," she said.

Do payers see partnerships as a way to ensure all patients get the best care? Rahman said as data show that only 5% of patients get care that conforms with NCCN guidelines, "it's clearly concerning."

The pandemic has awakened the entire health care landscape to how technology can be leveraged to better connect with patients, and payers see technology as a tool to "nudge members toward the right pathways that are associated with much higher clinically favorable outcomes." Certainly, in the next 3 to 5 years, she said, payers will be making greater use of technology to ensure members are receiving evidence-based care.

Virtual Care: Pick the Right Setting
West said the use of virtual care in oncology is not appropriate in every setting. "You can't do a good physical exam," he said. "And arguably, people would prefer to have their more emotional discussions in a live setting."

But for other uses, including routine management, virtual care can save patients a long drive to a cancer center. If it can be used to reduce disparities in access to subspecialty care needed in the age of precision medicine, it merits consideration.

"Telemedicine is a tool that we are just beginning to get a sense of how we might best use it, and I think it's not going to replace live visits, but it can be used alongside of them," West said. "And it has a great role that can really improve how we do care by distributing expertise across the geography far more than we can do with people driving to one center."
CANCER IS NO LONGER UNDERSTOOD as a disease of individual organs, but as a disease of pathways—the genetic and molecular patterns that direct how cancer cells adapt within the body. The era of precision oncology means clinicians no longer treat a single type of breast cancer or lung cancer, but a growing number of subtypes defined by the biomarkers that signal how cancer will behave.

This means the study of cancer—and the development of drugs to treat it—is increasingly one of finding smaller groups of patients. It also means the clinical trial designs of the past must adapt to the challenge of treating these patients where they are. The American Journal of Managed Care® recently convened experts from Cardinal Health Specialty Solutions to discuss current challenges in cancer trial designs and drug development, through the Oncology Value Coalition webinar series.

Moderator Bruce Feinberg, DO, chief medical officer at Cardinal Health Specialty Solutions, led the discussion with:

- Andy Klink, PhD, MPH, director, Real-World Evidence & Insights, Cardinal Health Specialty Solutions
- Ajeet Gajra, MD, MBBS, FACP, vice president and chief medical officer, Cardinal Health Specialty Solutions
- Scott Swain, PhD, MPH, director of Real-World Evidence and Regulatory Sciences, Cardinal Health Specialty Solutions

Evolution of Drug Development

Feinberg started with a discussion of the time and money required for drug development, particularly in oncology. It takes up to 12 years, and costs billions of dollars, to bring a new drug from bench to bedside. The traditional randomized control trial (RCT) design, which has been central to the development of evidence-based medicine, brings certain limitations.

"There is a problem in the representational nature of the research coming out of randomized controlled trials," Feinberg said. "Only about 3% of the advanced patient population with cancer in the United States is participating in trials, and of those who do participate, they are young longer, they are healthier, and they are less diverse." Patients in clinical trials also tend to be more health literate, which makes them less representative of the population.

This, combined with the current understanding of cancer as a disease of pathways, has made finding new roads to drug approval necessary and, in some cases, optimal.

Swain then discussed the rise of accelerated or expedited pathways, which arose in the 1990s out the activism of HIV patients and advocates, who sought a faster means of bringing life-saving drugs to market. The traditional clinical trial paradigm of phase 1, 2, and 3 had distinct strengths in proving a drug's safety and efficacy, but it was not a fast process. It became clear that viral load could serve as a surrogate marker, one highly predictive of survival, Swain said.

"We could get these drugs to patients sooner. So, in 1992, we got accelerated approval, and priority review," he said. There were other pathways that came later, "but this was the beginning of the recognition that, that if you have a very strong suspicion that a drug is going to work, and you have a patient population with great need, that there are now mechanisms in place to get drugs to those patients faster," while clinical studies continue.

Feinberg asked Gajra to comment on how 30 years after FDA launched the concept of accelerated approvals, “there doesn't seem to be a lot of appreciation or acceptance,” among physicians.

Gajra said there's no question the randomized phase 3 trial "remains the gold standard in the minds of physicians," and, in fact, these studies are important.

However, he said, the process "cannot be applied to every circumstance, every situation in a timely manner." In some cases, it's not only in the drug developer's interest but also the patient's, to use alternative pathways, "to get to that finish line faster."

Despite increased use of accelerated approvals, Gajra said, there remains a "generational gap" among physicians and scientists in their acceptance, because the traditional phase 1-2-3 design "has been the gold standard for so long."

FDA Efforts to Modernize Drug Evaluation

Feinberg then asked Klink whether he was seeing any shifts toward greater use of different kinds of evidence, including real-world evidence (RWE), in filings for drug approvals.

"Are you feeling like there is kind of the sea change, or it's still kind of dipping a toe in the water?" Feinberg asked.

Klink said the biopharma industry is gaining comfort "in exploring some of these ideas," with the main advantage being the amount of time that could be saved with RWE approaches. Swain noted that in the 1960s, when the phase 1-2-3 design was implemented, "there was a lot of confusion at the time—nobody really knew what to do."

"It reminded me a lot of how it was at FDA in 2016, when 21st Century Cures was passed—all the real-world evidence started flooding in; nobody really knew what they were doing. There was no guidance out," he said. Over the next few years, the agency has provided more direction, particularly with its 2018 framework document. ‘Swain noted that the accelerated approval options that arose in the 1990s came out of a specific need, and it took time to adapt them for other types of drugs.

Today, he said, there are alternative study designs, accelerated review, and accelerated approval. More critically, Swain said, "We've gone from a place where there was really one way to get a drug approved—you go through phase 1, then phase 2 and phase 3, and then you go through the normal review process. There's now almost an infinite number of combinations. ... You can really customize it based on your specific indication and your specific product."

He then reviewed the terms that have become well-known in oncology drug development. Fast track and breakthrough therapy designations are designed to increase communication with FDA, and make developers eligible for rolling and priority review. Swain explained that these are given when a drug is designed to treat a very serious disease for which no treatment exists or for a treatment that is far superior to a current treatment. Priority review can reduce decision time on a new drug application from 10 months to 6 months.

Adaptive study designs, he said, allow developers to prespecify study modifications than can allow for changing a dose or enrolling more patients from a certain subgroup if they have a stronger response. This is essential as cancer research moves beyond organ-level disease and dives deeper into looking at biomarkers; developers who see a group of patients responding to a drug can enroll more of them in a study.
In decentralized trials, providers make greater use of telemedicine and form partnerships with local health care providers. "So instead of going into the clinical site to see the physician, you may just see them on your phone or your iPad for most of your clinical visits," Swain said. "You may receive care locally; you may receive care in your home."

Feinberg asked Gajra what happens when the early hope of an accelerated approval doesn’t pan out. In the past year, FDA has addressed cases where accelerated approvals based on phase 2 results were withdrawn after results did not hold up in a later study.

"The spirit and the purpose of the accelerated approval track was appropriate when it was coined, and I think it’s appropriate today," Gajra said.

"There’s extreme dissemination of information compared with 30 years ago—so patients, families, advocacy groups—everyone’s very aware of any positive development anywhere in the world. And they certainly would like access to a given agent that might provide them some hope or fighting chance."

The Arrival of RWE
Klink reviewed how the 21st Century Cures Act of 2016 called on FDA to develop frameworks for using RWE in drug development. In the early 2000s, he said, it became clear that health systems were sitting on huge data sets that could be tapped for insights to identify patterns and drug signals. The Sentinel pilot program, which took place than 10 years ago, was an important milestone in using federal data to track drug safety.

"The quality and reliability of our real data has improved," Klink said, and evaluations for efficacy as well as safety began. "Even today, we can look at the COVID-19 vaccine rollout in the United States, where potential safety signals have been identified in a broader US population of those who receive the vaccine in the FDA is emergency with authorization. And given the low rates of these potential events, millions of doses were really required in order to identify these events, which may not have been possible in a traditional RCT setting."

FDA’s framework on real-world evidence, which outlined upcoming guidance for regulatory decision making, covers key areas, Klink said: (1) how to assess for real data sources; (2) study design considerations; and (3) analysis of world data.

Real-world data (RWD), he said, covers "data related to the patient health status or data relating to the delivery of health care routinely collected in a variety of sources, typically in routine clinical practice." RWD can include electronic health records, medical claims, and billing data, as well as patient generated data, such as survey or data from wearables, such as a Fitbit.

"One passive method of collecting real-world data is through routine medical encounters, where anytime a patient visits a health care facility, a claim may be generated, containing diagnoses, drug information and procedures, and that forms the basis of a longitudinal picture of health care encounters for that patient," Klink said.

**COMPARING RCTS TO RWE.** He then compared the benefits of RCTs compared with the use of RWE. "Causal inference is straightforward in RCTs," he said, but this can be a challenge with RWE, "due to randomization of treatment assignments between the 2 groups. RCTs have very rigid protocol, defined endpoints, and clear instructions on how they’re measured. Whereas in the [real-world data] setting, endpoints could be measured in precisely or using a variety of methods."

Using real-world data can come into play when an external control arm could be used alongside a single-arm trial. The external control arm, "may come about in a few different settings in which a parallel controller might not be feasible, or ethical. That might happen when the effect size of a new drug is expected to be large based on preliminary data, or the standard of care doesn’t exist."

**Using RWE in the Regulatory Process.** Convincing regulators to accept RWE as proof of efficacy can still be an uphill battle. But the pandemic has shown the need for greater flexibility and the need for alternative formats for drug development. RWE is still underutilized, Gajra said, "and I think some of this has just to do with the relative newness and the apprehensions."

"Manufacturers, of course, want to stick with a time-tested paradigm," he said, given the billions of dollars at stake. Lack of expertise in developing the data is another concern. "The drug development community needs to be educated and needs to understand how and where to best use real-world evidence, which can shorten time lines, which is their goal and can cut down on expenses, which is also their goal."

The key, he said, is to reach out to FDA early in the process. "This all has to be a part of that protocol," he said. "It has to be at the design stage. Otherwise, it’s too late."

**PMR VS PMC.** Swain then explained the difference between these postmarketing elements that may be required to obtain approval under an accelerated timeline. A postmarketing requirement (PMR) is a stricter standard than a postmarketing commitment (PMC), but both call for additional analyses that FDA will expect before granting full approval.

**WHAT FDA WANTS TO SEE.** Swain explained that when the first RWE studies were offered in regulatory processes, sometimes arrived without warning, and FDA if there was no prespecified protocol, the work was considered an ad-hoc analysis. The key questions, Swain said, are the following:

- Is there a prespecified protocol? Swain recommends giving FDA a proposal first, then a protocol.
- Do the scientific and regulatory questions align? In other words, does the RWE study population match the target population for the therapy. Will the study address regulatory questions and concerns? Are exposures and outcomes properly defined and identified?

Use of RWE presents its own challenges, including the risk of bias. Klink agreed with Swain that finding the right data set to answer the right regulatory question is essential. As Feinberg said, the key to using RWE is to talk to FDA "early and often."

**COVID-19 and Decentralized Trials**
Gajra noted the problem of the historic lack of representation in clinical trials. In oncology in particular, trial populations have not reflected the reality that cancer affects older adults. "As people get older, they have less mobility, they have less social support," he said.

Thus, enrolling these patients in trials becomes difficult, and when accrual is poor, it costs time and money for both the pharmaceutical company and for patients who need the drug. A more patient-centric approach, he said, is the decentralized trial, which makes it easier on the patient by allowing data collection to occur in their local physician’s office or even in their own homes. Patients are spared from having to travel for minor checkups or to sign paperwork. "There is no reason why it cannot be an electronic consent," Gajra said.

**FINDING SMALL GROUPS OF PATIENTS.** The decentralized approach, developed to study patients with rare diseases, will be needed for future cancer research, as cancer will increasingly be studied among small groups of patients with certain molecular markers. As with the accelerated approval process, Gajra said, protocols must be spelled out in advance. There are regulatory hurdles, he said, "but they are not insurmountable."

And for patients, there’s a significant improvement in quality of life. "If it’s infusion therapy, you’re sure, patients will always have to a clinic," he said. "But it doesn’t have to be a clinic that is 100 miles away, or from Staten Island to Upper East Side of Manhattan."

With the number of oral therapies, Gajra said, "there’s no excuse for not having decentralized design." Has COVID-19 helped move the ball forward? Swain said the situation with COVID-19 was unique, because federal funding allowed manufacturing of the vaccines to start "before we had proof they worked... But I think that could actually be implemented in cancer therapies, for example, where you know, you have a home run drug."

"I think what COVID really brought us was the acceleration of the decentralized design, because the same way that it influenced e-commerce, the same way that it influenced telework, it suddenly became necessary—and everybody figured out that we can do it, and then it works well." Swain said. "There’s evidence now that patients prefer it and the providers prefer it, because it’s much more convenient."

Feinberg asked if the recent controversy over some accelerated approvals would set back the cause of an expedited process. Swain said he did not think so. "I think what it really comes down to is the quality of your surrogate marker," he said. "I think that the call for amendments to the accelerated approval program is probably justified; I think there are things that could be done to improve it. But rather than getting rid of something, rather than taking a step back, I think it’s better to take a step forward and just move the process."

**REFERENCE**
NCCN Guidelines Add Zanubrutinib as Preferred Therapy for Waldenström Macroglobulinemia

LAURA JOSZT, MA

UPDated GUIDELINES from the National Comprehensive Cancer Network (NCCN) for Waldenström macroglobulinemia have added zanubrutinib (Brukinsa) as a preferred regimen.

The NCCN Guidelines Version 1.2022 Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma (WM/LPL) were updated to include zanubrutinib as a preferred regimen for the primary therapy of WM/LPL along with bendamustine/rituximab, bortezomib/dexamethasone/rituximab, ibrutinib ± rituximab, and rituximab/cyclophosphamide/dexamethasone. Preferred interventions are based on superior efficacy, safety, and evidence.1 Both zanubrutinib and ibrutinib ± rituximab are considered category 1 recommendations, which means they are based on high-level evidence and there is uniform NCCN consensus that the intervention is appropriate. The other therapies are all category 2A: based on lower-level evidence, but there is still uniform NCCN consensus that the intervention is appropriate.

Zanubrutinib was also added as a category 1 preferred regimen for previously treated WM/LPL. The other preferred regimens for previously treated WM/LPL are the same as the preferred regimens for primary treatment.

The addition of zanubrutinib to the guidelines was based on the findings from the ASPEN study published in Blood. The study compared the safety and efficacy of zanubrutinib, a novel highly selective Bruton tyrosine kinase (BTK) inhibitor, with ibrutinib, a first-generation BTK inhibitor.2

In ASPEN, 28% of patients on zanubrutinib and 19% on ibrutinib achieved a very good partial response (VGPR); no patient achieved a complete response (CR). The study did not meet the primary end point, which was proportion of patients achieving CR or VGPR, but the investigators noted that “there was a trend toward better disease control for zanubrutinib vs ibrutinib.”

Major response rate was similar (77% for zanubrutinib vs 78% for ibrutinib), as was progression-free survival (85% for zanubrutinib vs 84% for ibrutinib).

Patients on zanubrutinib had fewer instances of atrial fibrillation, contusion, diarrhea, peripheral edema, hemorrhage, muscle spasms, and pneumonia, as well as adverse events that led to treatment discontinuation.

“This study established that zanubrutinib is highly effective in the treatment of WM; zanubrutinib is associated with important safety advantages, especially with respect to cardiovascular toxicity,” the authors wrote.

The data from ASPEN was used in a supplemental new drug application (sNDA) with the FDA for zanubrutinib in the treatment of WM, which was submitted in February 2021. Health Canada approved zanubrutinib in WM in March based on the findings of ASPEN.

“We are pleased that the FDA has accepted the sNDA for Brukinsa in WM, a rare disease with significant morbidity,” Jane Huang, MD, chief medical officer, Hematology, BeiGene, said in a statement. “BTK inhibitors have transformed the treatment of WM in recent years, but discrepancies in response exist in patients with different subtypes, and toxicity can remain an issue.”3

REFERENCES

An ongoing trial is currently assessing the safety and tolerability of B7-H3 CAR T-cell therapy with temozolomide, with B7-H3 CAR T being injected between temozolomide cycles. Data from the study are expected in 2022.1

EGFRvIII CAR T-cell therapy is being studied in several trials, with an ongoing phase 1 study assessing the therapy in combination with temozolomide and another assessing EGFRvIII CAR T following radiosurgery in patients with recurrent GBM.

CAR T-cell therapy in combination with immune checkpoint inhibitors is also being assessed for both recurrent and resistant disease, say the investigators. A phase 1 trial is currently looking at the safety and efficacy of IL13Ralpha2-CRT T cells used alone or in combination with nivolumab and ipilimumab.

Although still in the preclinical stage, Fcγ-CRs T cells may prove to be a leader in the treatment of GBM and other solid tumors, say the investigators.

As research on CAR T-cell therapy in GBM progresses, the investigators are also calling attention to the challenges facing the therapy in the disease, including the highly unstable tumor microenvironment and the variable genetic nature of the disease.

“The mechanism by which the apparent tumor responses or growth delay in CAR-T cell-treated GBM are multifactorial. This cannot be attributed to the therapy but could instead result from differences in the natural history of disease between patients,” commented the investigators. "Although there are no direct ways to demonstrate the actual killing of tumor cells by CAR T in situ, previous clinical and preclinical data suggest that CAR-T-EGFRvIII cells induce their action by antigen-directed cytolysis after crossing the blood–brain barrier.”

REFERENCES

“Can we reduce cancer disparities through community engagement? A. Find out at Patient-Centered Oncology Care® September 23-24, 2021 | Omni Nashville Hotel Learn more: www.ajmc.com/pcoc-2021
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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.

Immune-mediated colitis:

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 discontinuation in 3 patients (0.4%) and required systemic corticosteroids in 2 patients (0.2%). Of these, 3 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence.

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 3 (0.4%) and Grade 2 (2.8%). Pneumonitis led to discontinuation of LIBTAYO in 2 patients (0.2%) and required systemic corticosteroids for 23 patients (2.9%). Of these, 1 patient (0.1%) died of respiratory failure.

Cytomegalovirus (CMV) infection/reactivation:

Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1–blocking antibodies. Patients with CMV infection/reactivation may require treatment with antiviral agents.

Thyroid dysfunction:

Thyroid dysfunction was not observed among patients receiving LIBTAYO.

Hypertension:

Hypertension has been observed in patients receiving LIBTAYO.

Hypothyroidism:

Hypothyroidism has been observed in patients receiving LIBTAYO.

Hepatitis:

Hepatitis 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 (cont’d)

Warnings and Precautions (cont’d)

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

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

Withhold or permanently discontinue LIBTAYO depending on severity. In general, if LIBTAYO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroids.

Immune-mediated pneumonitis: LIBTAYO can cause immune-mediated pneumonitis. In patients treated with other PD-1/PD-L1–blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 4 (0.5%), Grade 3 (0.5%), and Grade 2 (2.1%). Pneumonitis led to permanent discontinuation in 1.4% of patients and withholding of LIBTAYO in 2.1% of patients. Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 58% of the 26 patients. Of the 17 patients in whom LIBTAYO was withheld, 9 reinitiated after symptom improvement; of these, 3/9 (33%) had recurrence of pneumonitis. Withhold LIBTAYO for Grade 2, and permanently discontinue for Grade 3 or 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

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

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

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

For hepatitis with tumor involvement of the liver: Withhold LIBTAYO if baseline AST or ALT 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. Hypothyroidism led to withholding of LIBTAYO in 1.1% of patients. Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 8.3% of the 60 patients. Majority of the patients with hypothyroidism required long-term thyroid hormone replacement. Of the 9 patients in whom LIBTAYO was withheld for hypothyroidism, 1 reinitiated LIBTAYO after symptom improvement; 1 required ongoing hormone replacement therapy.

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

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

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

**Other immune-mediated adverse reactions:** The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 810 patients who received LIBTAYO or were reported with the use of other PD-1/PD-L1–blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

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

- **Nervous system:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, 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.
Important Safety Information (cont’d)

Warnings and Precautions (cont’d)

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

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

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

Complications of allogeneic HSCT
Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1–blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1–blocking antibody prior to or after an allogeneic HSCT.

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

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

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

Please see Brief Summary of Prescribing Information on the following pages.
5.1 Severe and Fatal Immune-Mediated Adverse Reactions

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of LIBTAYO. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. Immune-mediated adverse reactions can occur at any time after starting PD-1/PD-L1 blocking antibody. While the incidence of these reactions can vary with the dose and duration of therapy, the most severe reactions are likely to occur during the initial treatment and in patients with more aggressive disease.

Of the 5 patients in whom LIBTAYO was withheld for hepatitis, 3 patients reinitiated LIBTAYO after symptom improvement (3/16) required additional immunosuppression with mycophenolate. Hepatitis resolved in 50% of the 16 patients.

5.2 Immune-Mediated Nephritis with Renal Dysfunction

There was an increase in serum creatinine, which caused renal dysfunction. The definition of immune-mediated nephritis includes the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Immune-mediated nephritis occurred in 0.6% (5/810) patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Nephritis led to permanent discontinuation of LIBTAYO in 0.4% of patients. Immune-mediated nephritis required use of systemic corticosteroids or other immunosuppressants in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients.

Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Nephritis led to permanent discontinuation of LIBTAYO in 0.4% of patients. Immune-mediated nephritis required use of systemic corticosteroids or other immunosuppressants in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients.

Type 1 Diabetes Mellitus

Hypothyroidism occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypothyroidism led to permanent discontinuation of LIBTAYO in 0.1% (1 patient) and withholding of LIBTAYO in 0.1% (1 patient). Systemic corticosteroids were required in 67% (2/3) of patients with hypothyroidism. Hypothyroidism 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. Thyroiditis can also follow hypothyroidism. Initiate hormone replacement or medical management as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

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 0.1% of patients. Systemic corticosteroids were required in 0.3% (1 patient) with any thyroiditis 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%) adverse reactions. No patient discontinued treatment due to hyperthyroidism. Hyperthyroidism led to withholding of LIBTAYO in 0.5% of patients.

Systemic corticosteroids were required in 3.8% (1/26) of patients with hyperthyroidism. Hyperthyroidism resolved in 15% (4/26) of patients. Of the 2 patients, 2 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hyperthyroidism.

Hyperthyroidism: Hyperthyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%) adverse reactions. Hyperthyroidism led to withholding of LIBTAYO in 0.1% (1 patient). Hypothyroidism led to withholding of LIBTAYO in 1.1% of patients. Systemic corticosteroids were not required in any patient with hyperthyroidism. Hyperthyroidism resolved in 63% of the 60 patients. The majority of patients with hyperthyroidism required long-term thyroid hormone replacement.

Of the 9 patients in whom LIBTAYO was withheld for hyperthyroidism, 1 reinitiated LIBTAYO after symptom improvement. 1 required ongoing hormone replacement therapy.

Type 1 Diabetes Mellitus, which can present with diabetic ketoacidosis.

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withdraw LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

Type 1 diabetes mellitus occurred in 0.1% (1/810) of patients, including Grade 4 (0%) adverse reactions. No patient discontinued treatment due to Type 1 diabetes mellitus. Type 1 diabetes mellitus led to withholding of LIBTAYO in 0.1% of patients.

Immunodepressed Neutrophils with Renal Dysfunction

Immune-mediated neutrophils can cause immune-mediated neutrophilic reactions. The definition of immune-mediated neutrophilic reactions included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Immune-mediated neutrophilic reactions occurred in 2% (8/810) patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Neutrophils led to permanent discontinuation of LIBTAYO in 0.4% of patients and withholding of LIBTAYO in 0.8% of patients.

Systemic corticosteroids were required in all patients with neutrophils. Neutrophils resolved in 80% of the 5 patients. Of the 3 patients in whom LIBTAYO was withheld for neutrophils, 2 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of neutrophilia.

Immunodepressed Dermatologic Adverse Reactions

LIBTAYO can cause immune-mediated rash or dermatitis. The definition of immune-mediated dermatologic adverse reactions included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Immune-mediated dermatologic adverse reactions occurred in 1% (8/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%) adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 89% of the 13 patients. Of the 11 patients in which LIBTAYO was withheld for dermatologic adverse reactions, 7 reinitiated LIBTAYO after symptom improvement; of these, 43% (3/7) had resolution of the dermatologic adverse reaction.

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.

Cardio/Vascular: Myocarditis, pericarditis, vasculitis.

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve paresis, autoimmune encephalitis, seizures, vitrtis, and other ocular inflammation. Chorioretinitis, iritis, and other ocular inflammation. Some cases have been associated with fatal or near-fatal 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 visual 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: Hypophysitis.

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic recruristation lymphadenopathy (Kikuchi lymphadenopathy), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

5.3 Complications of Allogeneic HSCT

Fetal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with LIBTAYO. These complications can include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic artery thrombosis, veno-occlusive disease (VOD) and other rare complications (without an identified infectious cause). These complications may occur despite intervening therapy between transplant and initiation of or during treatment with LIBTAYO. If a complication occurs, identify and treat the underlying cause.

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

5.4 Embryo- Fetal Toxicity

Based on the mechanisms of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immunologically mediated rejection of the developing fetus resulting in fetal death. Advise women of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose (see Use in Specific Populations (8.1, 8.3)).
6. 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 CSCC (Studies 1540 and 1624), 130 patients with advanced BCC (Study 1620), 355 patients with NSCLC (Study 1624), and 164 patients with other advanced solid tumors (Study 1423). LIBTAYO was administered intravenously at doses of 3 mg/kg every 2 weeks (n=250), 300 mg every 3 weeks (n=543), or other doses (n=32; 1 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, 250 mg every 2 weeks). Among the 810 patients, 57% were exposed for ≥6 months and 25% were exposed for ≥12 months. In this pooled safety population, the most common adverse reactions (>15%) were musculoskeletal pain, fatigue, rash, and diarrhea.

The safety of LIBTAYO was evaluated in 219 patients with advanced CSCC (metastatic or locally advanced disease) in Study 1423 and Study 1540 (see Clinical Studies (7.1) in the full prescribing information). Of these 219 patients, 131 had mCSCC (median or distant) and 88 had cCSCC. Patients received LIBTAYO 1 mg/kg every 2 weeks (n=1), 3 mg/kg every 2 weeks (n=162) or 350 mg every 3 weeks (n=36) as an intravenous infusion until disease progression, unacceptable toxicity, or completion of planned treatment. The median duration of exposure was 38 weeks (2 weeks to 110 weeks).

The safety population characteristics were: median age of 72 years (38 to 96 years). 83% male, 96% White, and European Cooperative Oncology Group (ECOG) performance score (PS) of 0 (44%) and 1 (56%).

Serious adverse reactions occurred in 36% of patients. Serious adverse reactions that occurred in ≥1% of patients were pneumonitis, cutaneous, sepsis, and pneumonitis.

Permanent discontinuation due to an adverse reaction occurred in 8% of patients. Adverse reactions resulting in permanent discontinuation were pneumonitis, cough, pneumonitis, encephalitis, asptic meningitis, hepatitis, arthritis, musculoskeletal weakness, neck pain, soft tissue necrosis, complex regional pain syndrome, lymphadenopathy, rash, musculoskeletal pain, acne, skin abscess, and hypertension.

The most common (>20%) adverse reactions were fatigue, rash, diarrhea, musculoskeletal pain, and nausea. The most common Grade 3 or 4 adverse reactions (>2%) were cellulitis, anemia, hypertension, pneumonia, musculoskeletal pain, fatigue, pneumonitis, sepsis, skin infection, and hypercorticism. The most common (>4%) Grade 3 or 4 laboratory abnormalities worsening from baseline were lymphopenia, anemia, hyperglycemia, and hypophosphatemia.

Table 2 summarizes the adverse reactions that occurred in ≥10% of patients and Table 3 summarizes Grade 3 or 4 laboratory abnormalities worsening from baseline in ≥1% of patients receiving LIBTAYO.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LIBTAYO M=132</th>
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<tbody>
<tr>
<td>All Grades %</td>
<td>Grades 3-4 %</td>
</tr>
<tr>
<td>Fatigue</td>
<td>34</td>
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<tr>
<td>Skin and Subcutaneous Tissue</td>
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<tr>
<td>Rash</td>
<td>31</td>
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<td>Pruritus</td>
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<td>Gastrointestinal</td>
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<td>Diarrhea</td>
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<td>Nausea</td>
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<tr>
<td>Constipation</td>
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</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
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<tr>
<td>Musculoskeletal and Connective Tissue</td>
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<td>Musculoskeletal pain</td>
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<td>Arthritis</td>
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<td>Metabolism and Nutrition</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3-4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>2</td>
</tr>
<tr>
<td>Increased AST</td>
<td>2</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>2</td>
</tr>
<tr>
<td>Neurology</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>6</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>4</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LIBTAYO M=132</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades %</td>
<td>Grades 3-4 %</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>49</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>33</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
</tr>
<tr>
<td>Nausea</td>
<td>20</td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>20</td>
</tr>
<tr>
<td>Intestines and intestinal inflammation</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>16</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>15</td>
</tr>
<tr>
<td>Vasovagal syncope disorders</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
</tr>
<tr>
<td>Respiratory, nervous and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>11</td>
</tr>
<tr>
<td>Nausea disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea disorders</td>
<td>13</td>
</tr>
</tbody>
</table>

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v. 4.0B.
Table 5: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥ 1% of Patients with Advanced BCC Receiving Libtayo in Study 1620

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3-4 (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolytes</td>
<td></td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>3.1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3.5</td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin time prolonged</td>
<td>2.3</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Lympocite count decreased</td>
<td>2.3</td>
</tr>
</tbody>
</table>

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

Table 6: Adverse Reactions in ≥ 10% of Patients with Locally Advanced or Metastatic NSCLC Receiving Libtayo in Study 1624

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LIBTAYO N=355</th>
<th>Chemotherapy N=342</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td></td>
<td>Grades 3-4</td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
<td>Grades 3-4</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>3.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Grades 3-4</td>
</tr>
<tr>
<td>Rash</td>
<td>1.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Bladder and lymphatic system disorders</td>
<td></td>
<td>Grades 3-4</td>
</tr>
<tr>
<td>Anemia</td>
<td>5.0</td>
<td>3.6</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td>Grades 3-4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14.0</td>
<td>11.1</td>
</tr>
<tr>
<td>Metastasis and extension disorders</td>
<td></td>
<td>Grades 3-4</td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>1.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Vascular loss and embolism</td>
<td>5.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td>Grades 3-4</td>
</tr>
<tr>
<td>Cough</td>
<td>1.1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Twice was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (N.CTCAE) v.4.03.
a. Musculoskeletal pain is a composite term that includes back pain, arthralgia, pain in extremity, musculoskeletal pain, muscularkeletal chest pain, bone pain, myalgia, neck pain, spinal pain, and musculoskeletal stiffness.
b. Rash is a composite term that includes rash, dermatitis, urticaria, rash maculopapular, urticaria, rash erythematous, rash pruritic, psoriasis, atopic dermatitis, dermatitis acriform, dermatitis allergic, dermatitis atopic, dermatitis bullosus, drug eruption, dyshidrotic, eczema, folliculitis, pruritus, rash urticarial, and skin reaction.
c. Fatigue is a composite term that includes fatigue, asthenia, and malaise.
d. Pneumonia is a composite term that includes atypical pneumonia, embolitic pneumonia, lower respiratory tract infection, lung abscess, paracoccidian pneumonia, pneumonia, pneumonia bacterial, and pneumonia lobular.
e. Cough is a composite term that includes cough and productive cough.

Table 7: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in > 1% of Patients with Locally Advanced or Metastatic NSCLC Receiving Libtayo in Study 1624

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LIBTAYO N=355</th>
<th>Chemotherapy N=342</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td></td>
<td>Grades 3-4</td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
<td>Grades 3-4</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>3.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>2.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>2.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>0.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>1.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.7</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Hematology

Twice was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (N. CTCAE) v.4.03.
a. Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.

6.2 Immunoigcnity

As with all therapeutic proteins, there is a potential for immunoigcnicity. The detection of antibodiy formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibodiy (including neutralizing antibodiy) 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 antibodiy to cemiplimab-rwlc in the studies described below with the incidence of antibodiy in other studies or to other products may be misleading.

Anti-drug antibodiy (ADA) were tested in 823 patients who received Libtayo. The incidence of cemiplimab-rwlc treatment-emergent ADAs was 2.2% using an electrochemiluminescent (ECL) bridging immunoassay; 0.4% were persistent ADA responses. In the patients who developed anti-cemiplimab-rwlc antibodiy, there was no evidence of an altered pharmacokinetic profile of cemiplimab-rwlc.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

Animal reproduction studies have not been conducted with Libtayo to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-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-1 knockout mice. Based on its mechanism of action, fetal exposure to cemiplimab-rwlc may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

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

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

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

Of the 132 patients with BCC who received Libtayo in Study 1620, 27% were 65 years up to 75 years, and 32% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.
Zanubrutinib Improves Outcomes Compared With Ibrutinib in R/R CLL/SLL, ALPINE Study Shows

INHIBITION OF BRUトン TYROSINE KINASE (BTK) has transformed the treatment of chronic lymphocytic leukemia (CLL). While ibrutinib has led the way, zanubrutinib, a next-generation BTK inhibitor, has the potential to change treatment again.

Zanubrutinib improves outcomes and reduces toxicity because it minimizes off-target inhibition of TEC- and EGFR-family kinases, which is seen with ibrutinib, explained Peter Hillmen, PhD, MBChB, professor at the University of Leeds and honorary consultant hematologist at Leeds Teaching Hospitals NHS Trust.

Hillmen presented the interim results of the phase 3 ALPINE study during the Presidential Symposium at the European Hematology Association 2021 Virtual Congress (EHA2021 Virtual). ALPINE is a global, randomized, phase 3 study comparing zanubrutinib with ibrutinib in patients with relapsed/refractory (R/R) CLL/small lymphocytic leukemia (SLL). In the preplanned interim analysis, the data cutoff occurred at 12 months after randomization of the first 415 patients.

The patients were randomized 1:1 to receive either zanubrutinib 160 mg twice a day (n = 207) or ibrutinib 420 mg once a day (n = 208). The baseline patient and disease characteristics were well balanced between the 2 arms, according to Hillmen.

The primary endpoint was overall response rate (ORR), defined as partial response (PR) plus complete response. Secondary end points were atrial fibrillation, duration of response, progression-free survival (PFS), overall survival (OS), time to treatment failure, PR with lymphocytosis or higher, patient-reported outcomes, and safety.

ORR was “definitely superior” for zanubrutinib, Hillmen said. The ORR for zanubrutinib was 78.3% (95% CI, 72.0%-83.7%) vs 62.5% (95% CI, 55.5%-69.1%) for ibrutinib. The 12-month PFS was 94.9% for zanubrutinib vs 84.0% for ibrutinib. At 18 months, 20 patients on zanubrutinib had progressive disease compared with 42 patients on ibrutinib. OS wasn’t significantly different: 97.0% for zanubrutinib vs 92.07% for ibrutinib.

The majority of patients had an adverse event (AE), but zanubrutinib had fewer AEs leading to discontinuation (7.8% vs 13.0%) and fewer deaths due to AEs (3.9% vs 5.8%). Zanubrutinib had a slightly higher rate of neutropenia (28.4% vs 21.7%), but grade ≥3 infections were lower (12.7% vs 17.9%).

The interim analysis also evaluated atrial fibrillation/flutter, which was a prespecified safety end point. The rate was significantly lower with zanubrutinib (10.1%) compared with ibrutinib (16.0%).

“These data support that more selective BTK inhibition, with more complete and sustained BTK occupancy, results in improved efficacy and safety outcomes than a less-specific BTK inhibitor,” Hillmen concluded.

In the Q&A, one attendee asked about comparing the results of ALPINE with ELEVATE-RR, which was presented a week earlier at the annual meeting of the American Society of Clinical Oncology. In that phase 3 trial comparing acalabrutinib with ibrutinib in patients with relapsed/refractory CLL, acalabrutinib had a noninferior PFS and significantly fewer events of atrial fibrillation.

Comparing the two is challenging for a number of reasons, though. Hillmen noted that the second-generation BTK inhibitors are not exactly the same as one another, so it wouldn’t be surprising to see differences in terms of toxicity or efficacy. In addition, ALPINE has interim data with a median duration of 15 months compared with ELEVATE-RR’s 3 years.

“We need to see more maturity in this trial to really compare,” Hillmen said. The ALPINE abstract was submitted to the meeting as a late-breaking abstract, so the data are still being analyzed.

However, one thing was apparent from both trials: “[T]he tolerability of the second-generation BTK inhibitors…is improved,” Hillmen said.

Pair of Studies Highlight Zanubrutinib Tolerability, Efficacy, Utility

BUILDING ON POSITIVE RESULTS PRESENTED at last year’s American Society of Hematology annual meeting, a pair of studies presented at EHA2021 Virtual, this year’s annual meeting of the European Hematology Association, added heft to the advantages of zanubrutinib over other Bruton tyrosine kinase (BTK) inhibitors for several hematologic cancers.

Zanubrutinib is a second-generation BTK inhibitor known to have fewer off-target effects among both treatment-naive and treatment-experienced patients. It is currently approved for use in patients with mantle cell lymphoma (MCL), while the FDA has accepted a supplemental new drug application (sNDA) for Waldenstrom macroglobulinemia (WM) with a projected Prescription Drug User Fee Act target date of October 18, 2021. In addition, zanubrutinib’s sNDA for its use among adults with marginal zone lymphoma (MZL) received a priority review designation in May.

The first study, which took place in China, encompassed 91 patients with a median age of 61 years (range, 35-87) who had relapsed/refractory (R/R) chronic lymphocytic leukemia (n = 82) or small lymphocytic leukemia (n = 9) (CLL/SLL). Their most common poor prognostic indicators were unmutated IGHV (56.0%), del(17p) or TP53 mutation (24.2%), and del(11q) (22%). A high response rate was seen among those with del(17p) and/or TP53 mutation (91.9%; 95% CI, 70.8%-99.9%), while all with del(11q) responded (100%; 95% CI, 83.2%-100%).

These results add to data previously published from the same trial, which demonstrated that zanubrutinib had a favorable benefit-risk profile.

In the present phase 2 study, patients received zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity. By the end of the follow-up period (median, 33.9 months; range, 0.8-41.4), 34.1% of patients had discontinued treatment because of progressive disease or adverse events. However, 65.9% remained on zanubrutinib. Overall, 69.2%, 12.1%, and 6.6% had a partial response (PR), PR with lymphocytosis, or complete response, respectively; 3.3% each had stable or progressive disease or discontinued treatment before the first assessment; and 2.2% were not evaluable. In total, 87.9% (95% CI, 79.4%-93.8%) of the entire study cohort had a response.

With additional primary efficacy end points of duration of response (DOR) and progression-free survival (PFS), the authors’ analyses revealed:

• 24-month DOR: 83.4% (95% CI, 73.2%-90.6%)
• 36-month DOR: 69.9% (95% CI, 57.8%-79.6%)
• 24-month PFS: 85.0% (95% CI, 70.5%-91.7%)
• 36-month PFS: 68.1% (95% CI, 56.6%-77.4%)

The most common nonhematologic and hematologic adverse effects (AEs) were upper respiratory tract infection in 56.0% of patients and neutropenia in 78.0%, respectively.

Results of the second study, the BGB-3111-215 trial, support using zanubrutinib as a treatment option following previous treatment failure. These preliminary results were seen among 44 patients who received zanubrutinib (either 160 mg twice daily or 320 mg once daily) following intolerance to the first-generation BTK inhibitors ibrutinib (n = 39) or acalabrutinib (n = 1), with 4 patients having received both. Among this cohort, 34 had CLL, 6 had WM, and 2 each had MCL and MZL. Their median age was 70.5 years (range, 49.0-91.0), and all received at least 1 zanubrutinib dose post enrollment.

Data accumulated up to the November 1, 2020, cutoff showed that among the 44 patients, 43 were still on treatment. Among those who previously were

REFERENCE
on ibrutinib or acalabrutinib, 82.8% and 77.8%, respectively, did not have a recurrence of intolerant events, of which there were 87 with ibrutinib and 9 with acalabrutinib. This breaks down to a median 2 per patient (range, 1-5).

Among the patients who did have an intolerant event recur, the events were of a lower severity in 86.7% of previous-ibrutinib patients and 50% of previous-acalabrutinib patients.

Following administration of zanubrutinib in the patients, no deaths were reported. However, 77.3% did report an AE (myalgia, 20.5%; confusion, 18.2%; dizziness, 15.9%; fatigue, 15.9%; cough, 11.4%); 13.6% reported a grade ≥3 AE, and 2.3% reported a serious AE. In addition, 13.6% and 4.5% required dose interruption and dose reduction, respectively. No patients required treatment stoppage.

Overall, all patients with efficacy data available maintained response (38.5%) or had a deepening response (61.5%) to the newer BTK inhibitor. “Zanubrutinib provided an additional treatment option after intolerance to other BTK inhibitors,” the authors concluded, “demonstrating tolerability and sustained or improved efficacy.”

References

New Phase 2 Results From MAGNOLIA Are Positive for Zanubrutinib

AN UPDATED ROUND OF RESULTS from MAGNOLIA involving zanubrutinib in marginal zone lymphoma (MZL) was presented at the European Hematology Association 2021 Virtual Congress (EHA2021 Virtual). MAGNOLIA is a single-arm, multicenter, phase 2 study of adults with relapsed/refractory MZL who were previously treated with at least 1 prior line of therapy, including at least 1 CD20-directed regimen.

In MAGNOLIA, patients were treated with 160 mg of zanubrutinib twice daily until disease progression or unacceptable toxicity. Use of long-term antplatelet and anticoagulation agents is permitted. The primary end point is the overall response rate (ORR) as determined by an independent review committee. Secondary end points include ORR by investigator assessment, duration of response (DOR), progression-free survival (PFS), and safety.

Results through August 2020 presented at the American Society of Hematology in December 2020 showed that patients taking zanubrutinib, a Bruton tyrosine kinase (BTK) inhibitor, seemed to tolerate the drug better than earlier-generation BTK inhibitors, which allowed them to stay on the drug. The new round of results presented at EHA, which include data through January 11, 2021, include 68 patients enrolled and treated, with a median age of 70 years, including 28 who were 75 years or older.

MZL subtypes seen in the study included 38% of patients with extranodal MZL, 38% nodal, 18% splenic, and 6% indeterminate MZL. Patients in the study had received a median of 2 prior therapies, and 32% had disease that was refractory to their last therapy.

Results presented at EHA showed:

- Patients were exposed to the drug for a median of 59.1 weeks (range, 3.7-84.1). Almost all (66/68) were evaluable.
- At a median follow-up of 15.5 months (range, 1.6-21.7), investigator-assessed ORR, including complete response (CR) and partial response (PR), was 74%. This included 24% CR and 50% PR; 17% had stable disease.
- Responses were observed in all subtypes, with an ORR of 68% in extranodal, 84% in nodal, 75% in splenic, and 50% in indeterminate subtypes. The CR rate was 36% for extranodal MZL, 20% for nodal, 8% for splenic, and 25% for indeterminate subtype.
- Median DOR and PFS were not reached. At 15 months, PFS was 68%; the 12-month DOR was 81%.
- Adverse events. Since the last round’s data cutoff, 2 patients in the study died from COVID-19 pneumonia and 1 patient who had preexisting coronary artery disease died from a heart attack. None of the deaths were considered related to zanubrutinib.
- Of the 66 patients who could be evaluated, 28 (41%) stopped treatments, including 20 due to disease progression, 1 who withdrew consent, and 3 who required prohibited medications. Four stopped treatment due to adverse events (AEs), including the 2 who had COVID-19 pneumonia and the patient with the heart attack; the last one stopped due to pyrexia attributed to disease transformation.
- The most common (≥10%) treatment-emergent AEs reported were diarrhea (22%), bruising (21%), constipation (15%), pyrexia (13%), abdominal pain (12%), upper respiratory tract infection (12%), back pain (10%), and nausea (10%). Most AEs were grade 1 or 2.

Phase 2 Results in Mantle Cell Lymphoma From Study in China

Long-term data from a phase 2 study in China evaluating zanubrutinib in patients with relapsed/refractory mantle cell lymphoma (MCL) were presented during the EHA2021 Virtual Congress. The study’s 86 patients had a median follow-up of 33.3 months, with data cutoff in September 2020.

The patients, who were enrolled in 13 centers across China, had a median age of 60.5 years, and 83.7% were considered intermediate-to-high risk based on the International Prognostic Index Score. Most patients had advanced MCL, with 90.7% having stage III or higher; 45.3% had bone marrow involvement and 70.9% had extranodal disease. They had a median of 2 prior lines of therapy, and 52.3% had refractory disease.

Patients in the single-arm study were given 160 mg of zanubrutinib twice a day until disease progression or unacceptable toxicity. Responses were measured every 12 weeks until week 96, and then every 24 weeks. The ORR, PFS, overall survival, and safety were assessed. Results were as follows:

- With a median follow-up of 33.3 months, 45.4% of patients remained on the study drug and 54.7% had stopped taking it, mostly due to disease progression (43.0%) or adverse events (9.3%).
- The ORR was 83.7%, and 67 patients (77.9%) achieved CR. Median DOR was not reached; 57.3% of the responders were estimated to be event-free—no disease progression or death—at 30 months.
- Median PFS was 33.0 months, and responses were generally consistent across all subgroups analyzed, including level of prior therapy and refractory status.

Adverse events. Consistent with earlier results, the treatment-related AEs that occurred most frequently, in at least 20% of the patients, were decreased neutrophil count (46.5%), upper respiratory tract infection (38.4%), rash (36.0%), decreased white blood cell count (33.7%), and decreased platelet count (32.6%). Most of these events were grade 1 or 2. The most common grade 3 events were decreased neutrophil count (18.6%) and pneumonia (12.8%).

Most of the AEs were seen during the initial treatment stage with zanubrutinib, and very few events were reported during the latest follow-up period.

References
Investigators Report Survival, Cost-effectiveness Data for Zanubrutinib

TREATMENT WITH ZANUBRUTINIB VS BENDAMUSTINE-RITUXIMAB (BR) or dexamethasone-rituximab-cyclophosphamide (DRC) in patients with Waldenström macroglobulinemia (WM) has demonstrated longer survival, and zanubrutinib appears more cost-effective than ibritinib, according to poster presentations at the European Hematology Association 2021 Virtual Congress.

WM is a rare, indolent, B-cell lymphoma that is generally treated with rituximab-based regimens or Bruton tyrosine kinase inhibitors.

Survival Findings
To compare progression-free survival (PFS), overall survival (OS), and adverse events (AEs) among regimens, investigators used matching-adjusted indirect comparisons (MAICs) to match and compare data for 3 groups of patients with WM: 101 patients (83 relapsed/refractory, 19 treatment-naïve) treated with zanubrutinib in the ASPEN trial; 71 relapsed/refractory patients treated with BR; and 72 treatment-naïve patients treated with DRC.1

MAICs carry the limitation of not being able to completely adjust for all unobserved and unreported baseline patient characteristics.

Investigators said zanubrutinib vs DRC demonstrated significantly longer 12- and 24-month PFS (92% vs 85% and 90% vs 68%, respectively), longer 12- and 24-month OS (95% vs 92% and 94% and 85%), and a higher incidence of neutropenia (14.3% vs 9.7%). The postmatching HR for zanubrutinib PFS was 0.35 (95% CI, 0.14-0.86) and OS was 0.47 (95% CI, 0.14-1.62).

Zanubrutinib vs BR demonstrated significantly longer 12- and 24-month PFS (94% vs 79% and 81% vs 59%, respectively) and 12- and 24-month OS (98% vs 87% and 88% vs 77%), along with significantly lower incidence of neutropenia (17.5% vs 35.2%).

The postmatching HR for zanubrutinib vs BR PFS was 0.37 (95% CI, 0.15-0.91); for OS, it was 0.29 (95% CI, 0.10-0.85).

Zanubrutinib Cost-Effectiveness
Investigators concluded that zanubrutinib appears to be cost-effective vs ibritinib for US patients with WM who have received a1 prior therapy or as first-line treatment.2

They estimated savings based on life-years (LYs), quality-adjusted life-years (QALYs), and costs for each treatment over 30 years, basing OS, PFS, and time-to-discontinuation on data from the ASPEN trial. Costs considered included drug acquisition, management of AEs, and terminal care.

Findings demonstrated 0.94 LY and 0.84 QALY gained for patients treated with zanubrutinib vs ibritinib and an incremental cost of $11,132 for zanubrutinib treatment, based on costs associated with extended treatment for zanubrutinib vs ibritinib ($1,547,630 vs $1,536,498, respectively). Total LYs for zanubrutinib vs ibritinib were 11.33 vs 10.39, respectively, and total QALYs were 8.75 vs 7.90.

With its longer time to treatment failure and a lower monthly drug acquisition cost, zanubrutinib reduces costs of disease management by $2935 and other direct terminal costs by $2964 vs treatment with ibritinib, the authors said. The incremental cost-effectiveness ratio for QALY gained was $13,205, according to the study.

Investigators said that at a willingness-to-pay threshold of $100,000 per QALY gained, the probability of zanubrutinib being cost-effective was 61%.

A limitation of this economic analysis was the immature survival data from ASPEN, the authors said.

REFERENCES

The Role of CAR NK Cells: Competition or Complement to CAR T-Cell Therapy?

CHIMERIC ANTIGEN RECEPTOR (CAR) T-cell therapy has revolutionized treatment for some hematological malignancies, and hundreds of trials are investigating CAR T-cell therapies in hematology and oncology. However, these therapies are complex to produce.

CAR-engineered natural killer (CAR NK) cells may be an alternative that compete with and complement CAR T-cell therapy, explained Ulrike Köhl, MD, PhD, during a plenary session at the European Hematology Association 2021 Virtual Congress (EHA2021 Virtual). She is a professor of immune oncology and director of the Institute for Clinical Immunology at the University of Leipzig, and director of the Fraunhofer Institute for Cellular Therapeutics and Immunology, both in Leipzig, Germany.

Interest is growing in CAR NK cells, with 20 trials worldwide in 2019: Half were directed against CD19, and the other half against different cancer epitopes. That number has risen to 35 in 2021.

In the case of both CAR T cells and CAR NK cells, effector cells cannot recognize cancer cells to start killing them, but transduction of the respective effector cells results in a new receptor that is upregulated on the surface and binds to the cancer cell, killing it. The benefits of CAR T-cell therapies in diseases like acute lymphocytic leukemia (ALL) and diffuse large B-cell lymphoma have become well known. There are approximately 800 trials worldwide, Köhl said.

“But we are also aware that manufacturing these autologous personalized CAR T cells is very complex,” Köhl said. The process includes stimulation, transduction, expansion, and formulation and takes about 12 days, on average, but it can take as long as 22 days.

Quality control is also challenging, and the CAR T-cell product can fail. Study results indicate that the product fails in somewhere between 1% and 12% of patients, and possibly in even up to 17% of patients.

“What’s the reason for that? [It’s that] these are heavily pretreated patients with a limited bone marrow function [and] less functional and [more] exhausted T cells,” Köhl explained.

With NK cells, experience with allogeneic NK cell trials have shown a good graft vs leukemia effect without graft-vs-host disease (GVHD), Köhl said. A study of NK cell trials found that interleukin (IL)-2 stimulation led to improved NK cell cytotoxicity, but tumor immune escape was a disadvantage.

Köhl gave the example of a child with acute myeloid leukemia (AML) in an early relapse state, who reached complete remission 1 month after NK cell application. “Unfortunately, this did not last very long, due to tumor immune escape mechanism,” she said.

Trials that redirected NK cells showed improved results. For instance, in ALL, donor NK cells that were activated with cytokines against ALL cells killed 70% of the leukemic cells, and when the NK cells were redirected, they could completely eliminate ALL cells, according to Köhl.

Similar results were seen in AML, where activated NK cells had good activity against AML cells, but redirected CAR NK cells “killed much better.”

Interest is growing in CAR NK cells, with 20 trials worldwide in 2019: Half were redirected against CD19 and the other half against different cancer epitopes. That number has risen to 35 in 2021.

The first-in-human trial in the United States led by Katy Rezvani, MD, PhD, at the University of Texas MD Anderson Cancer Center, tested CAR NK cells in patients with relapsed/refractory B-cell lymphoid malignancies; the cells were
Celltrion Releases First Real-World Data for Its Rituximab Biosimilar in DLBCL

CELLTRION HEALTHCARE RELEASED new real-world data demonstrating the clinical effectiveness of its biosimilar rituximab (Truxima; CT-P10) in patients with diffuse large B-cell lymphoma (DLBCL) at the European Hematology Association 2021 Virtual Congress (EHA2021 Virtual).

Truxima received marketing authorization from the European Medicines Agency in 2017 for the treatment of rheumatoid arthritis and certain blood cancers, including DLBCL. The most common subtype of non-Hodgkin lymphoma (NHL), DLBCL represents an estimated 30% to 40% of adult cases. Truxima was the first rituximab biosimilar approved in the United States, launching on the US market in 2019 in partnership with Teva Pharmaceutical Industries.

Celltrion ran a noninterventional postauthorization safety study in which researchers collected patient data from hospital medical records for 382 patients with DLBCL who received CT-P10 therapy in the United Kingdom, Spain, France, Germany, or Italy. Treatment pattern data were retrospectively collected during a 30-month observation period.

"This is the first multicountry retrospective postapproval study to investigate the effectiveness and safety of CT-P10 treatment in patients with DLBCL in a real-world setting across Europe," said Mark Bishton, PhD, consultant hematologist and honorary clinical associate professor at the University of Nottingham School of Medicine in the United Kingdom, in a statement.

The results met the primary end points of overall survival, progression-free survival, and summary of best responses. Thirty months after receiving their first dose of CT-P10, 67% (95% CI, 61.3%-72.1%) of patients had not experienced disease progression, and the overall survival was 74% (95% CI, 69.2%-79.1%).

Additionally, 82% (n = 312) of patients achieved a complete response and 12% (n = 46) achieved a partial response 30 months post index. Only 4% (n = 16) experienced no response and 2% (n = 8) experienced disease progression.

Secondary end points for CT-P10’s safety profile and treatment pathways were also examined. Patients generally found CT-P10 to be tolerable, and the number of adverse events reported was comparable with that reported for the reference product (Rituxan).

Celltrion also released real-world data on rapid infusion of CT-P10 in 192 patients with NHL and chronic lymphocytic leukemia (CLL) at the EHA Updates-in-Hematology. Typically, infusion of rituximab in Europe is conducted through a slow initial infusion rate with a gradual upward titration. Rapid infusion is often reserved for when patients receive subsequent infusions after experiencing no serious complications after the first dose.

This was the first multicountry study to report real-world evidence evaluating the safety and efficacy of rapid infusion of CT-P10. The results showed that rapid infusion of the biosimilar was well tolerated, with only 10% (n = 20; 95% CI, 6.0%-15.0%) of patients reporting an infusion-related reaction (IRR).

"We need both," she said. "They clearly have also different roles." CAR NK cells, for instance, may possibly be used as a bridge to transplantation.

REFERENCE
When is TAZVERIK® (tazemetostat) appropriate for your relapsed or refractory (R/R) follicular lymphoma (FL) patient?

TAZVERIK is indicated for the treatment of:

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

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).1

EZH2=enhancer of zeste homologue 2.

Important Safety Information

- **Warnings and Precautions**
  - **Secondary Malignancies**
    The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 729 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL). Monitor patients long-term for the development of secondary malignancies.
  - **Embryo-Fetal Toxicity**
    Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk.

Important Safety Information continued on back page of this insert. Please see Brief Summary of the Prescribing Information on the adjacent pages.
TAZVERIK (tazemetostat) tablets 200mg BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONSULT THE PACKAGE INSERT FOR COMPLETE PRESCRIBING INFORMATION.

INDICATIONS AND USAGE
- TAZVERIK (tazemetostat) is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.
- TAZVERIK is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options. These indications are approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies]. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial.

DOSE AND ADMINISTRATION

Patient Selection—Select patients with relapsed or refractory (R/R) follicular lymphoma (FL) for treatment with TAZVERIK based on the presence of EZH2 mutation of codons Y646, A682, or A692 in tumor specimens [see Clinical Studies]. Information on FDA-approved tests for the detection of EZH2 mutation in relapsed or refractory follicular lymphoma is available at: http://www.fda.gov/CompanionDiagnostics.

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

Dose Modifi cations for Adverse Reactions—Table 1 summarizes the recommended dose reductions, and Table 2 summarizes the recommended dosage modifi cations of TAZVERIK for adverse reactions.

Table 1. Recommended Dose Reductions of TAZVERIK for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia [see Adverse Reactions]</td>
<td>Neutrophil count less than 1 x 10^9/L</td>
<td>• Withhold until neutrophil count is greater than or equal to 1 x 10^9/L or baseline. For first occurrence, resume at same dose. For second and third occurrence, resume at reduced dose. Permanently discontinue after fourth occurrence.</td>
</tr>
<tr>
<td>Thrombocytopenia [see Adverse Reactions]</td>
<td>Platelet count less than 50 x 10^9/L</td>
<td>• Withhold until platelet count is greater than or equal to 75 x 10^9/L or baseline. For first and second occurrence, resume at reduced dose. Permanently discontinue after third occurrence.</td>
</tr>
<tr>
<td>Anemia [see Adverse Reactions]</td>
<td>Hemoglobin less than 8 g/dL</td>
<td>• Withhold until improvement to at least Grade 1 or baseline, then resume at same or reduced dose.</td>
</tr>
<tr>
<td>Other adverse reactions [see Adverse Reactions]</td>
<td>Grade 3</td>
<td>• Withhold until improvement to at least Grade 1 or baseline. For first and second occurrence, resume at reduced dose. Permanently discontinue after third occurrence.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>• Withhold until improvement to at least Grade 1 or baseline. For first occurrence, resume at reduced dose. Permanently discontinue after second occurrence.</td>
</tr>
</tbody>
</table>

Dosage Modifi cations for Drug Interactions

Strong and Moderate CYP3A Inhibitors—Avoid coadministration of TAZVERIK with strong or moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the TAZVERIK dose as shown in Table 3 below. After discontinuation of the moderate CYP3A inhibitor for 3 elimination half-lives, resume the TAZVERIK dose that was taken prior to initiating the inhibitor [see Drug Interactions, Clinical Pharmacology].

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

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

CONTRAINDICATIONS—None.

WARNINGS AND PRECAUTIONS

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

Embryo-Fetal Toxicity—Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC(0-24)] at the 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose [see Use in Specific Populations].

ADVERSE REACTIONS—The following clinically significant adverse reactions are described elsewhere in labeling: Secondary Malignancies [see Warnings and Precautions], Clinical Trial Experience—Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of TAZVERIK was evaluated in two cohorts (Cohorts 4 and 5) of Study E7438-G000-101 that enrolled patients with relapsed or refractory follicular lymphoma [see Clinical Studies]. Patients received TAZVERIK 800 mg orally twice daily (n=99). Among patients who received TAZVERIK, 68% were exposed for 1-6 months or longer, 39% were exposed for 12 months or longer, and 21% were exposed for 18 months or longer. The median age was 62 years (range 36 to 87 years), 54% were male, and 95% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. The median number of prior therapies was 3 (range 1 to 11). Patients were required to have a creatinine clearance ≥40 mL/min per the Cockcroft and Gault formula. Serious adverse reactions occurred in 30% of patients who received TAZVERIK. Serious adverse reactions in ≥2% of patients who received TAZVERIK were general physical deterioration, abdominal pain, pneumonia, sepsis, and anemia. Permanent discontinuation due to an adverse reaction occurred in 6% of patients who received TAZVERIK. Adverse reaction resulting in permanent discontinuation in ≥2% of patients was secondary primary malignancy. Dosage interruptions due to an adverse reaction occurred in 28% of patients who received TAZVERIK. Adverse reactions requiring dosage interruptions in ≥3% of patients were thrombocytopenia and fatigue. Dose reduction due to an adverse reaction occurred in 9% of patients who received TAZVERIK. The most common adverse reactions (≥20%) were fatigue, upper respiratory tract infection, musculoskeletal pain, nausea, and abdominal pain. Table 6 presents adverse reactions in patients with relapsed or refractory follicular lymphoma in Cohorts 4 and 5 of Study E7438-G000-101.

Table 6. Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Follicular Lymphoma Who Received TAZVERIK in Cohorts 4 and 5 of Study E7438-G000-101

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAZVERIK N=99</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>30</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>17</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>20</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>22</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>17</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Respiratory and mediastinal system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>17</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAZVERIK*</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>50</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>50</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Decreased white blood cells</td>
<td>41</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>20</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>53</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>24</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>21</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>18</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>17</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAZVERIK*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>50</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>50</td>
</tr>
<tr>
<td>Decreased white blood cells</td>
<td>41</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>20</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>53</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>24</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>21</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>18</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>17</td>
</tr>
</tbody>
</table>

**DRUG INTERACTIONS**

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

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

**USE IN SPECIFIC POPULATIONS**

**Pediatric Use** - No dose adjustment of TAZVERIK is recommended for patients with liver function impairment. No dose adjustment of TAZVERIK is recommended for patients with renal function impairment. No dose adjustment of TAZVERIK is recommended for patients with mild (<50 mL/min) or moderate (≥50 mL/min to <60 mL/min) hepatic impairment. No dose adjustment of TAZVERIK is recommended for patients with mild (<40 mL/min) or moderate (≥40 mL/min to <50 mL/min) or severe (>50 mL/min) renal impairment. TAZVERIK is not recommended for patients with severe renal impairment or those with creatinine clearance <40 mL/min.

**Hepatic Impairment** - No dose adjustment of TAZVERIK is recommended for patients with mild (<50 mL/min), moderate (≥50 mL/min to <60 mL/min), or severe (>60 mL/min) hepatic impairment.

**CONTRAINDICATIONS**

TAZVERIK is contraindicated in patients with moderate or severe renal impairment or those with creatinine clearance <40 mL/min.

**Warnings and Precautions**

Females of reproductive potential - Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK.

**Reproductive Toxicity**

TAZVERIK may decrease the efficacy of hormonal contraceptives. Avoid coadministration of strong or moderate CYP3A inhibitors with hormonal contraceptives. Coadministration of TAZVERIK with hormonal contraceptives may decrease the efficacy of hormonal contraceptives. Avoid coadministration of strong or moderate CYP3A inhibitors with hormonal contraceptives.

**Drug Interactions**

TAZVERIK may decrease the efficacy of hormonal contraceptives. Avoid coadministration of strong or moderate CYP3A inhibitors with hormonal contraceptives.

**Adverse Reactions**

TAZVERIK may decrease the efficacy of hormonal contraceptives. Avoid coadministration of strong or moderate CYP3A inhibitors with hormonal contraceptives.

**Use in Specific Populations**

Females of reproductive potential - Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK.

**Special Populations**

Females of reproductive potential - Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK.

**Pediatric Use**

TAZVERIK is not recommended for pediatric patients due to potential for serious adverse reactions.

**Hepatic Impairment**

TAZVERIK is not recommended for patients with mild (<50 mL/min), moderate (≥50 mL/min to <60 mL/min), or severe (>60 mL/min) hepatic impairment.

**CONTRAINDICATIONS**

TAZVERIK is contraindicated in patients with moderate or severe renal impairment or those with creatinine clearance <40 mL/min.

**Warnings and Precautions**

Females of reproductive potential - Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK.

**Reproductive Toxicity**

TAZVERIK may decrease the efficacy of hormonal contraceptives. Avoid coadministration of strong or moderate CYP3A inhibitors with hormonal contraceptives. Coadministration of TAZVERIK with hormonal contraceptives may decrease the efficacy of hormonal contraceptives. Avoid coadministration of strong or moderate CYP3A inhibitors with hormonal contraceptives.

**Drug Interactions**

TAZVERIK may decrease the efficacy of hormonal contraceptives. Avoid coadministration of strong or moderate CYP3A inhibitors with hormonal contraceptives.

**Adverse Reactions**

TAZVERIK may decrease the efficacy of hormonal contraceptives. Avoid coadministration of strong or moderate CYP3A inhibitors with hormonal contraceptives.
Important Safety Information (continued)

Embryo-Fetal Toxicity (continued)
Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC 0-45h]) at the 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose.

Adverse Reactions
In 99 clinical study patients with relapsed or refractory follicular lymphoma receiving TAZVERIK 800 mg twice daily: Serious adverse reactions occurred in 30% of patients who received TAZVERIK. Serious adverse reactions occurring in ≥2% were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. The most common (≥20%) adverse reactions were fatigue (36%), upper respiratory tract infection (30%), musculoskeletal pain (22%), nausea (24%), and abdominal pain (20%).

Drug Interactions
Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK, which may decrease the efficacy of TAZVERIK. Coadministration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates.

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

Before prescribing TAZVERIK, please read the Brief Summary of the Prescribing Information on the adjacent pages.

EZH2=enhancer of zeste homologue 2; MT=mutant type; WT=wild type.

References: 1. TAZVERIK (tazemetostat) Prescribing Information. Cambridge, MA: Epizyme, Inc., July 2020. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-cell Lymphomas V.3.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed April 1, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
Amgen US Biosimilar Trends Report Highlights Price Discounts

NO NEW BIOSIMILARS have been approved so far in 2021, and the number of approvals in 2020 (3) was low compared with previous years; but 6 years after its first biosimilar launch, the United States is ahead of where the European Union was, according to a preview of Amgen’s 2021 Biosimilar Trends Report.

Further, biosimilars are launching at deep discounts to reference products and capturing increasing market share, the preview stated.

“The rate of biosimilar uptake is generally increasing over time... Additionally, first-to-launch biosimilars tend to capture a greater portion of [market share] compared with later entrants.”

The European Union approved its first biosimilar in 2006 (somatropin), and 6 years later, the European market had just 11 biosimilars approved vs 29 for the United States.

Although 8 of the 29 approved US biosimilars won’t be launched before 2023, that leaves 21 biosimilars in the marketplace so far. The only biosimilar launched in 2021 has been Ribi, Amgen’s rituximab agent. The FDA approved Ribi for marketing in December 2020.

“Data show that the US biosimilar landscape is advancing faster than the European Union biosimilar landscape [did],” according to the Amgen preview. There are currently 65 biosimilars approved in the European Union.

The full 2021 Biosimilar Trends Report is expected to be published in autumn 2021.

Pricing Trends
The preview measures the difference in wholesale acquisition costs (WACs) for biosimilars vs originator drugs. WACs are the list prices that manufacturers charge wholesalers, although these do not include rebates and discounts provided by the manufacturer, which are important for a precise understanding of what wholesalers are paying.

WACs for biosimilars are sometimes well below WACs for reference products, according to Amgen. For example, the WAC for Avsola (infliximab: Amgen) was 57% below the reference product (Remicade) price WAC when the biosimilar was launched in July 2020.

Four pegfilgrastim biosimilars were launched from July 2018 to June 2020, and these were issued at WAC discounts of 33% to 37%, according to the preview. During that time, the average selling price (ASP) for the originator product, Neulasta, dropped by 35%. The ASP is the manufacturer average price minus rebates and discounts.

In the case of infliximab biosimilars, the discounts have been significantly deeper with each successive biosimilar introduced to market. However, the time period involved (late 2016 to mid-2020) was longer, and ASP prices for the reference product, Remicade, have dropped roughly 47% since the first infliximab biosimilar launch.

The introduction of trastuzumab biosimilars, from July 2019 to April 2020, was marked by significantly more modest WAC discounts of 10% to 22%, according to the report. Meanwhile, the reference product (Herceptin) ASP dropped 5% or less, Amgen said.

Amgen also compared biosimilar WACs with reference product ASPs, demonstrating that, at the wholesale level, biosimilars were introduced for less than reference product prices net of discounts or rebates.

The most dramatic example was for the filgrastim biosimilar Nivestym, which was introduced at a WAC 24% below the reference product (Neupogen) ASP.

Biosimilar prices are decreasing at an annual rate of 10% to 15%, the preview noted.

Market Share
The report also stated that biosimilars launched in the past 2 years have achieved a significantly larger average market share (61%) vs biosimilars launched prior to 2019 (13%). “The rate of biosimilar uptake is generally increasing over time... Additionally, first-to-launch biosimilars tend to capture a greater portion of [market share] compared with later entrants,” Amgen said.

Filgrastim biosimilars have captured the largest share of their respective market (73%); infliximab biosimilars, the lowest (23%).

REFERENCE
Neulasta but did not directly address the advertising message the FDA has objected to.

“There is a robust body of clinical and real-world evidence that demonstrates that when used every cycle, Neulasta significantly reduced the incidence of febrile neutropenia (FN) as well as FN-related events, including FN-related hospitalization and the use of anti-infective drugs in patients undergoing chemotherapy,” Amgen said in a statement to The Center for Biosimilars.

The study cited is inadequately designed and precludes the drawing of conclusions regarding the comparative risk of FN in patients taking Amgen’s pegfilgrastim products depending on delivery method. It likewise does not support conclusions about any other FDA-licensed pegfilgrastim products. The company noted it has a $2-billion stake in biosimilars, implying that running them down would not be to its benefit.

Amgen said the FDA’s concerns relate to a banner ad directed at health care providers about a “real-world evidence” study for Neulasta used in both the Onpro and prefilled syringe study arms.

The ad did not make sufficiently clear that Neulasta, Amgen’s originator product, was also used in the PFS arm, and so merely using the nonproprietary name pegfilgrastim could tarnish biosimilars by association, the FDA contends.

The FDA also takes issue with the following claims used in the advertisement:

- “In a real-world study with nearly 11,000 patients, pegfilgrastim prefilled syringe
resulted in a significantly higher risk of FN vs Onpro.”
- “Across all cycles of chemotherapy, the incidence of FN associated with prefilled syringe was 1.7% (n = 455) vs 1.3% (n = 126) for Neulasta Onpro.”
- “With [prefilled syringe], FN incidence increased by 31% vs Onpro.”

In addition, the FDA contends that “multiple limitations” of the retrospective study used to justify these assertions makes such assertions very unsound.

The FDA also contends Amgen cannot fairly state that the alleged higher risk of FN with prefilled syringe reached the level of statistical significance.

“The use of an unvalidated algorithm with unknown performance characteristics is a significant limitation because of the potential for misclassification of patients at the onset of the study,” the agency wrote.

It said the algorithm chosen to select study participants relied on diagnosis codes for neutropenia and fever or infection and no information was provided to the FDA’s Office of Prescription Drug Promotion about the sensitivity or positive predictive value of the algorithm or diagnostic codes.

“It cannot be ruled out that selection bias is a barrier to access to safe, effective and lower-cost biosimilars,” said Meaghan R. Smith, executive director of the Biosimilars Forum.

REFERENCE

FDA notifies Amgen of misbranding of its biological product Neulasta due to false or misleading promotional communications about the product’s benefits.


Former JHL Biotech Officials Are Indicted in Theft of Trade Secrets From Genentech

TWO FORMER OFFICIALS of JHL Biotech, formerly of Zhubei, Taiwan, are alleged to have stolen trade secrets relating to biosimilar manufacture from Genentech, and a former Genentech principal scientist and her husband have pleaded guilty to conspiring to assist them, according to an unsealed indictment and statement from the US Attorney’s Office for the Northern District of California.

Raco Ivanov Jordanov, 73, of Rancho Santa Fe, California, cofounder and former CEO of JHL and Rose Lia, 72, of South San Francisco, California, another company cofounder and former company chief operating officer, are alleged to have also committed wire fraud exceeding $101 million.

The unsealed indictment alleges that the pair worked with insiders at Genentech in San Francisco, California, to steal thousands of confidential and proprietary documents from Genentech that enabled JHL to accelerate its development and production of biosimilars of Genentech agents. JHL is alleged to have used the advantage it gained to obtain a lucrative biosimilar development deal with Sanofi.

At the time, JHL was working on biosimilars for the cancer therapies rituximab (Rituxan), trastuzumab (Herceptin), and bevacizumab (Avastin).

 Alleged Scheme

The indictment stated that the scheme began in 2009 when Lin recruited a scientist at Genentech and her husband to steal confidential information. Those scientists helped JHL to “cut corners, reduce costs, solve problems, save time, and otherwise accelerate product development timelines,” the indictment stated.

The alleged perpetrators were said to have taken documents covering Genentech’s standard operating procedures and pasted JHL logos over them and passed them off as JHL standard procedures. The partnership with Sanofi, a Paris, France–based company, was for the manufacture and distribution of biosimilars in China. That deal was signed in 2016.

“Sanofi allegedly paid $101 million to JHL Biotech, using foreign and interstate wires to carry out the corporate transaction. This cash payment allegedly was part of a strategic relationship worth potentially $337 million to JHL Biotech,” the indictment stated.

Upon disclosure of some of the aspects for the above-described allegations, in 2019, JHL’s stock valuation, once as high as $916 million, crashed. The company later renamed itself and divided into 2 companies: Eden Biologics and Chime Biologics, both of Wuhan, China.

In tandem with the indictment, the US Attorney’s Office also indicated that Xanthe Lam and her husband, Allen Lam, who worked in the Quality Control Department at Genentech, have pleaded guilty to conspiracy and other charges related to the theft of trade secrets from Genentech.

REFERENCE

CONSIDERATIONS FOR PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

PSMA: A POTENTIAL PHENOTYPIC BIOMARKER IN PROSTATE CANCER

PSMA may bring the potential of phenotypic precision medicine to the mCRPC population

- Highly expressed in >80% of men with advanced prostate cancer
- Can be detected noninvasively by PSMA-targeted PET/CT imaging, which has shown high sensitivity and specificity in detecting tumor lesions
- Is a potential therapeutic target associated with oncogenic signaling pathways that promote cell proliferation, cell survival, and angiogenesis


mCRPC, metastatic castration-resistant prostate cancer; PET/CT, positron emission tomography/computed tomography; PSMA, prostate-specific membrane antigen.

*Clinical significance has not been established and research is ongoing.

References
CMS Seeks Changes to Radiation Oncology Model, ASTRO Responds

ONCE AGAIN, THE RADIATION ONCOLOGY (RO) Model1 is targeted for changes under CMS’ annual rulemaking for the Medicare Hospital Outpatient Prospective Payment System (HOPPS) and Ambulatory Surgical Center (ASC) Payment System. For several years, CMS has tried to implement a model that would test whether making site-neutral payments to physician practices, including free-standing radiation therapy centers, would “preserve or enhance” care quality while reducing Medicare spending.

However, the head of the organization representing radiation oncologists criticized CMS’ plans. Thomas J. Eichler, MD, chair of American Society for Radiation Oncology (ASTRO), declared, “Access to radiation therapy for people with cancer is under attack.”

The RO Model has been discussed since 2014. ASTRO has said it agrees with the concept of value-based care, but the group has disagreed with CMS on reimbursement levels and whether to make the model mandatory. Then, in the wake of unprecedented disruption and missed screenings due to the COVID-19 pandemic,2 implementation of a 5-year performance period under the RO Model was extended: first under the 2021 interim final rule and again under the Consolidated Appropriations Act, 2021. The appropriations act delayed the start of the RO Model until January 1, 2022.3

“By proposing to cut high-value radiation treatments by as much as 22% and proceeding with more than $160 million in reductions under the [Radiation Oncology] Model, CMS is jeopardizing the ability of the nation’s radiation therapy professionals to continue to provide essential care for their patients now and the future.”

—Thomas J. Eichler, MD, chair, American Society for Radiation Oncology

Previously, CMS had divided episode payments under the RO Model into the professional component and the technical component. Professional component services are those that can only be provided by a physician; the technical component includes services, equipment, supplies, and other costs.1 On July 19, 2021, CMS’ proposal for the 2022 Medicare HOPPS and ASC Payment System Rule addressed a number of areas that have been affected by the COVID-19 public health emergency, including the RO Model. According to a summary from CMS, the proposed 2022 rulemaking puts forth the following:4

- The 5-year performance period for the RO Model would begin on January 1, 2022, and end on December 31, 2026.
- The baseline period would shift from 2016-2018 to 2017-2019.
- Discounts would be lowered to 3.5% for the professional component and 4.5% for the technical component.
- Brachytherapy would be removed from the list of modalities under the RO Model; it would be paid under fee-for-service.
- Cancer inclusion criteria would be revised, and liver cancer would not meet the criteria for the model.
- If a beneficiary switches from Medicare to Medicare Advantage during an episode before treatment is complete, CMS would deem the episode incomplete, and radiation therapy would be paid for at the traditional Medicare rate.
- CMS would adopt an “extreme and uncontrollable circumstances” policy, which would offer flexibility to limit reporting and other administrative burdens of RO Model participation; payment would be adjusted as necessary.

In its proposal, CMS calls for excluding hospital outpatient departments that are taking part in the Community Transformation track of the CHART Model from participation in the RO Model. In these cases, the same policy for overlap between the RO Model and the Medicare Shared Savings Program would apply. In his statement, ASTRO’s Eichler asked why CMS has “singled out” radiation oncology for payment cuts when cancer incidence rates are rising, following the delayed screenings seen during the pandemic.

“By proposing to cut high-value radiation treatments by as much as 22% and proceeding with more than $160 million in reductions under the RO Model, CMS is jeopardizing the ability of the nation’s radiation therapy professionals to continue to provide essential care for their patients now and in the future,” Eichler said. “Access to life-saving cancer treatments will suffer, and the viability of clinics already reeling from the pandemic will be at considerable risk if these proposals are finalized.”

ASTRO called on President Joe Biden, given his history of advocacy for patients with cancer, to intervene in changing the RO Model proposals and other Medicare Physician Fee Schedule cuts. Eichler said that the group would once again appeal to Congress for direct relief if its plea to the Biden administration is not successful.

The radiation oncologists, Eichler said, are “committed to value-based care and to constructively engaging with CMS on reasonable ways to improve these policies. We are eager to help President Biden achieve his goal of ending cancer as we know it, and we are developing promising approaches to reduce health care disparities in cancer treatment. These difficult policy challenges require investments in our human and technological cancer care infrastructure that would be virtually impossible under the current proposals.”

REFERENCES


Next-Generation Oncology APMs Need More Planning to Succeed

THE ONCOLOGY CARE MODEL (OCM) from CMS’ Center for Medicare & Medicaid Innovation was originally supposed to expire on June 30, 2021, to be replaced by Oncology Care First. However, in light of the COVID-19 pandemic, that date was pushed back by 1 year—and this may be a good thing.

Value-based care is at the core of the OCM, due to the ever-increasing costs of cancer care. In the 5 years since the OCM was originally implemented on July 1, 2016, however, its results have been mixed. The reasons, experts point out, may include the model’s complexity, that it may not be all about the patient, and potential outlier costs.

“Medicare did not go into this to improve the quality of cancer care,” said Michael Kolodziej, MD, vice president and chief innovation officer at ADVI Health, a health care and life sciences consulting company. “They went into this to save money.”

Kolodziej added that performance measures are “so confusing that many practices do not fully understand how they have managed to generate savings, which deprives them of the confidence that they can continue to succeed in the model.”

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A Viewpoint published July 1, 2021, in JAMA Oncology adds to the discussion by highlighting challenges that the OCM has encountered over the past 5 years, then proposing solutions to enable next-generation alternative payment models (APMs) to succeed in the precision medicine era.1 •

REFERENCE
1. Mullangi S, Schleicher SM, Parikh RB. The Oncology Care Model at 5 Years—value-based payment in the precision medicine era. JAMA Oncol. Published online July 1, 2021. doi:10.1001/jamaoncol.2021.1512

ZUMA-7 Results Underscore Axi-Cel’s Efficacy for LBCL

ON JUNE 28, 2021, Kite announced topline results for ZUMA-7, a randomized phase 3 multicenter study of axicabtagene ciloleucel (axi-cel, Yescarta), which showed that the chimeric antigen receptor (CAR) T-cell therapy improved event-free survival (EFS) by 60% (HR, 0.398; P < .0001) over chemotherapy and stem cell transplant among patients with second-line relapsed or refractory large B-cell lymphoma (LBCL).

The study began in 2017 as the first randomized clinical trial to test earlier use of a CAR T-cell therapy against standard of care (SOC) and had a median follow-up time of 2 years—the longest of any study in this setting. A total of 359 patients aged 22 to 81 years were initially enrolled in 77 centers around the world. More than 30% of participants were 65 years or older. Results show that the study met its primary end point of EFS and its secondary end point of objective response rate.

Interim analyses also revealed an overall survival trend favoring axi-cel, but further analyses are warranted as data were immature. More detailed results are slated to be presented at a future medical congress, and Kite, a Gilead company, plans to initiate discussions with regulators regarding submission of a supplemental biologics license application to expand the treatment’s currently approved indications.

The trial was also conducted under a Special Protocol Agreement with the FDA, meaning its design, clinical end points, and statistical analysis were all agreed upon in advance with the agency. Participants received a 1-time infusion of axi-cel and outcomes were compared with those who received SOC treatment, defined as a reintroduction of immunochemotherapy. If the patient responded and could tolerate more treatment, they then received high-dose chemotherapy and stem cell treatment.

“The top-line results of the randomized ZUMA-7 trial paint the picture of a potential paradigm shift in the treatment of large B-cell lymphoma,” Frederick L. Locke, MD, the trial’s lead investigator and coleader of the Immuno-Oncology Program at Moffitt Cancer Center in Tampa, Florida, said in a statement.

“The outcomes for patients relapsing after frontline chemotherapy in this study are dramatically improved with rapid referral [to a CAR T-center] and a single infusion of axicabtagene ciloleucel as compared with chemotherapy and consolidative autologous transplant, the longstanding second-line standard of care,” Locke said.

The investigators found:

• 6% of patients experienced grade 3 or higher cytokine release syndrome (CRS), with a median onset of 3 days;
• 21% of patients experienced grade 3 or higher neurological events; and
• no new safety concerns were identified in this second-line setting.

Axi-cel is currently not approved by any agency to treat patients in the second-line setting, although about 40% of patients with LBCL will need second-line treatment because their cancer will relapse or become refractory.

In addition, the treatment is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) and is indicated for adult patients in 2 categories: those with relapsed or refractory LBCL after 2 or more lines of systemic therapy, and those with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy.

The REMS program mandates that “health care facilities that dispense and administer [axi-cel] must be enrolled and comply with the REMS requirements and must have on-site, immediate access to a minimum of 2 doses of tocilizumab for each patient for infusion within 2 hours after [axi-cel] infusion, if needed for treatment of CRS.”

REFERENCE

Preclinical Research Sets the Stage for Potential of CAR NK-Cell Therapy in Hematologic Malignancies

AS THE SCIENTIFIC COMMUNITY continues to determine ways to improve the efficacy and safety of chimeric antigen receptor (CAR) T-cell therapy, some research has looked at the potential of engineering a different type of cell to try and fight cancer: natural killer (NK) cells. In a recent review, investigators looked at the available data on the treatment approach across hematologic malignancies.

In their review, the investigators explained that NK cells are effector cells in the immune system and that engineering them can improve their antitumor abilities. The treatment approach could address some of the obstacles associated with CAR T-cell therapy, including the need to generate autologous CAR T-cell production for each specific patient and the therapy’s economic implications. Unlike CAR T cells, CAR NK cells can be produced from allogeneic donors. CAR NK cells also carry a lower risk of cytokine release syndrome—a well-documented adverse effect of CAR T-cell therapy.

However, the investigators also noted that CAR NK-cell treatment comes with its own set of challenges.

“Extensive research over the last few decades has shown the safety and credibility of using NK cells to treat cancer. However, NK-cell therapy is still vulnerable to immunosuppressive mechanisms,” they wrote. “To resolve immunosuppression, improve cancer cell targeting, and finally enhance the antitumor effects of NK cells in cancer immunotherapy, acceptable and effective gene manipulation systems are required.”

The investigators noted that advanced efforts are underway to address and mitigate these key challenges and that with these efforts—and the promising results seen in preclinical models—CAR NK-cell treatments are on track to have “a strong and important contribution [to] cancer therapy.”

Preclinical research includes exploration in both leukemias and lymphomas—a large group of malignancies that come with diverse outcomes and prognoses. So far, results show that CAR NK-cell treatment can treat the diseases by targeting antigens such as CD19, CD20, CD7, and CD5.

Some research has also shown that CAR NK-92 cells can overcome B-cell acute and chronic leukemia resistance to parental NK cells, while other in vitro research of NK-92 cells showed promise in chronic lymphocytic leukemia. In aggressive T-cell leukemias, investigators have shown that delivering CD5- or CD3-targeting CARs into the NK-92 cell line can elicit cytotoxic activity against both primary T-cell lymphoma cells and T-cell leukemia cell lines. CAR NK cells may also help overcome challenges resulting from treatment of heterogenous acute myeloid leukemia (AML), according to the investigators.

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Cell Therapy Can Prevent Infections in Immunocompromised Patients With Leukemia

ROMYELOCEL-L, A TREATMENT of ready-made human immune cells, can prevent infections in patients treated for leukemia who have a weakened immune system, according to the results of a phase 2 trial published in the Journal of Clinical Oncology.

The investigators evaluated a single infusion of romyelocel-L in immunocompromised patients with acute myeloid leukemia (AML) who were undergoing intensive chemotherapy. Romyelocel-L consists of immature, human-derived immune cells that work to replenish neutrophils and help fight or prevent infections.

"This cell therapy has great potential to help patients with [acute myeloid leukemia] by reducing their infections, length of hospital stays, use of antibiotics, and development of antibiotic residence."

—Pinkal Desai, MD, assistant professor of medicine, Division of Hematology and Medical Oncology, Charles, Lillian, and Betty Neuwrith Clinical Scholar in Oncology, New York Presbyterian/Weill Cornell Medical Center

"The current standard of care [cytarabine- and anthracycline-based induction regimens] for younger and fit older patients results in serious infections and an early mortality rate of 7% to 11% despite administration of antimicrobials," the authors explained.

The investigators conducted a multicenter, randomized, open-label, phase 2 study of romyelocel-L plus granulocyte colony-stimulating factor (G-CSF; treatment arm) vs G-CSF monotherapy (control arm) in patients receiving induction chemotherapy. The goal was to reduce chemotherapy-induced neutropenia. Patients in the treatment arm received an infusion of romyelocel-L on day 9, 10, or 11.

A total of 163 patients were enrolled from 21 US centers, and 120 patients were evaluable: 59 and 61 in the treatment and control arms, respectively. Only 6.8% of patients in the treatment group experienced infections compared with 27.9% in the control group. Patients in the treatment group spent less time in the hospital (average of 25.5 days) compared with the control group (average of 28.7 days).

"This cell therapy has great potential to help patients with AML by reducing their infections, length of hospital stays, use of antibiotics, and development of antibiotic resistance—leading to improved outcomes for them overall," said lead author Pinkal Desai, MD, assistant professor of medicine in the Division of Hematology and Medical Oncology; the Charles, Lillian, and Betty Neuwrith Clinical Scholar in Oncology at Weill Cornell Medicine; and an oncologist at NewYork-Presbyterian/Weill Cornell Medical Center.

Although the study met the end points showing lower incidence of infection, antibiotic use, and days of hospitalization in the treatment arm, there was no reduction in the mean duration of febrile episodes.

Patients receiving romyelocel-L had less frequent treatment-emergent significant adverse events (SAEs). All but 1 SAE were considered not related to romyelocel-L. No patient on romyelocel-L had graft-vs-host disease or new-onset platelet refractoriness, nor did any have to be discontinued from the study because of an SAE or an AE.

"[Because] infection remains the most common cause of morbidity and mortality in patients with AML, strategies to reduce the risk of infection are an unmet need," the authors concluded. "These results provide the foundation for a phase 3 trial with the primary end point of reduction in infections during intensive induction chemotherapy for adults with AML."

MRD-Guided Decisions May Aid Postremission Treatment Choices in 1 Type of AML

MAKING CLINICAL DECISIONS for patients with intermediate-risk acute myeloid leukemia (IR-AML) based on their measurable residual disease (MRD) following remission may help facilitate better treatment optimization, according to results of a new study.

Based on subgroup analyses of more than 500 patients aged 14 to 60 years with IR-AML, the investigators say that MRD-guided decisions may be associated with better treatment stratification and improved postremission treatment. They note that prospective multicenter trials are needed to validate these findings.

According to the investigators, while MRD has been widely adopted as a stratification tool for treatment, the association of dynamic MRD with treatment following remission in these patients is not well understood.

"It remains a challenge for practitioners to choose the optimal [postremission treatment] for patients with IR-AML because different conclusions have been drawn in previous reports," explained the investigators. They noted that although some research results have indicated that patients with IR-AML may fare better with allogeneic stem cell transplant (allo-SCT), other results show that chemotherapy or autologous SCT (auto-SCT) may yield better survival.

The study had a few important findings, including as follows:

- Among patients who were MRD negative following induction therapy, those who received chemotherapy and auto-SCT achieved better graft-vs-host-disease-free, relapse-free survival than those who received allo-SCT.
- Among patients who had persistent MRD and recurrent MRD, those who received allo-SCT had superior disease-free survival and overall survival (OS) than those who received auto-SCT or chemotherapy.
- Among patients who achieved MRD negativity following 2 cycles of chemotherapy, those who received either type of SCT had better disease-free survival and OS compared with those receiving chemotherapy.
- Among patients who achieved MRD negativity following 3 cycles of chemotherapy, those receiving allo-SCT had more favorable survival.
Based on the findings, the investigators suggest that [chemotherapy] and auto-SCT might be preferable for the persistent MRD-negative patients, and allo-SCT should be strongly recommended for the persistent MRD-positive and recurrent MRD-positive patients. Auto-SCT prior to allo-SCT might be recommended for the patients who were MRD negative after 2 cycles of chemotherapy. Allo-SCT might be preferable for the patients who were MRD negative after 3 cycles of chemotherapy.

Throughout the study period, 146 of the patients relapsed, with a median time from the first course of chemotherapy to relapse of 10.9 months. Patients receiving allo-SCT had the longest time to relapse with a median time to relapse of 13.0 months compared with a median 9.19 months among patients receiving auto-SCT and a median 9.9 months among patients receiving chemotherapy.

**REFERENCE**


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**Obesity, Disparities, and Treatment Advancements Shape US Cancer Trends**

**RESULTS OF THE LATEST** Annual Report to the Nation on the Status of Cancer show that although overall cancer death rates in the United States continue to decline—especially for lung cancer and melanoma—for some forms, including prostate, colorectal, and female breast cancers, death rates continue to increase, or declines have slowed or even leveled off.

Several risk factors, including obesity, lack of physical activity, and increased consumption of alcohol, appear to be fuelling certain cancer trends, according to the report.

The findings underscore the need for increased prevention, early detection, and treatment efforts, in addition to broad, equitable interventions focused on underresourced populations, authors wrote. Results were published in *JNCI: The Journal of the National Cancer Institute.*

Data reflect mortality trends reported from 2001 to 2018 in the United States and were compiled via a collaboration among the American Cancer Society, CDC, National Cancer Institute, and North American Association of Central Cancer Registries. Cancer incidence data represent cases reported between 2001 and 2017. All trends reflect data collected prior to the COVID-19 pandemic.

"The declines in lung cancer and melanoma death rates are the result of progress across the entire cancer continuum—from reduced smoking rates to prevent cancer to discoveries such as targeted drug therapies and immune checkpoint inhibitors," said Karen E. Knudsen, PhD, MBA, the CEO of the American Cancer Society.

Despite numbers showing a decrease in cancer death rates for men and women from all racial and ethnic groups, overall cancer incidence grew among females, children, and adolescents and young adults. However, for children younger than 15 years and individuals aged 15 to 29 years, death rates did decrease despite increased incidence.

Analyses revealed:

- Overall cancer incidence rates (per 100,000 population) for individuals of all ages between 2013 and 2017 were 487.4 among males and 422.4 among females.
- During this period, incidence rates remained stable among males but slightly increased in females (average annual percent change [AAPC], 0.2%; 95% CI, 0.1%-0.2%).
- Overall cancer death rates (per 100,000 population) during 2014-2018 were 185.5 among males and 133.5 among females.
- During this period, overall death rates decreased in both males (AAPC, –2.2%; 95% CI, –2.5% to –1.9%) and females (AAPC, –1.7%; 95% CI, –2.1% to –1.4%).
- Death rates decreased for 11 of the 19 most common cancers among males and for 14 of the 20 most common cancers among females, but they increased for 5 cancers in each sex.
- Between 2014 and 2018, the declines in death rates accelerated for lung cancer and melanoma, slowed down for colorectal and female breast cancers, and leveled off for prostate cancer.
- 2-year relative survival for distant-stage skin melanoma was stable for those diagnosed between 2001 and 2009 but increased by 3.1% (95% CI, 2.8%-3.5%) per year for those diagnosed between 2009 and 2014, with comparable trends among males and females.

For both sexes, death rates increased for brain and pancreas cancers, and some nervous system cancers, while rates also increased for oral cavity and pharynx cancers in males and liver and uterus cancers in females. Causes of increased deaths associated with cancers of the brain and nervous system are unclear and warrant additional research.

Cancer incidence rates continue to increase among females and adolescents and young adults, authors wrote. This fact, and the stabilized rates among males after earlier declines, largely reflect changes in cancer risk factors, notably increases in excess body weight, they explained.

Although trends reflect scientific advances yielding outcome differences at the population level, "I believe we could achieve even further improvements if we address obesity, which has the potential to overtake tobacco use to become the leading modifiable factor associated with cancer," noted Norman E. "Ned" Sharpless, MD, the director of the National Cancer Institute at the National Institutes of Health.

Total daily sitting time, in addition to the "staggering" rise in obesity among adults and youth, could impede efforts to decrease rates of associated cancers.

"The increase of breast cancer incidence is largely driven by hormone receptor-positive cancer, which may in part reflect continuing reduction of parity rates, advanced age at first birth, the obesity epidemic [which contributes to postmenopausal breast cancer], high levels of physical inactivity, and increase of alcohol consumption," authors explained.

Poor outcomes for uterine, prostate, and kidney cancers are also all linked, in part, with obesity.

"When it comes to race, breast cancer death rates are 40% higher among Black women than White women, regardless of similar incidence rates. Uterine cancer death rates are also twice as high among Black women, authors noted.

Overall cancer incidence rates were slightly lower among Black vs White individuals, while overall cancer death rates were higher among Black people. According to authors, the latter trend can be attributed to multiple factors including tumor biology, stage at diagnosis, receipt of timely and effective care, and systemic discrimination in cancer care delivery.

"It is encouraging to see a continued decline in death rates for many of the common cancers," said Karen Hacker, MD, MPH, the director of the CDC's National Center for Chronic Disease Prevention and Health Promotion.

However, "to dismantle existing health disparities and give everyone the opportunity to be as healthy as possible, we must continue to find innovative ways to reach people across the cancer care continuum—from screening and early detection to treatment and support for survivors," she said.

Social determinants of health, such as exposure to cancer risk factors and limited access to healthy food, safe places for physical activity, and evidence-based preventive services exacerbate incidence and mortality trends.

"When evaluating health disparities, it is critical to acknowledge the social factors that influence the health of the communities and access to health care," said Betsy A. Kohler, MPH, the executive director of the North American Association of Central Cancer Registries.

"Social and economic indicators, particularly based on small area assessments, are increasingly important to understanding the burden of cancer."
Following Approval of Ruxolitinib, Relative Survival of pMF Has Slightly Increased

OVER THE PAST FEW DECADES, the relative survival (RS) of primary myelofibrosis (pMF) has increased, according to a new study offering data from a real-world setting on how the arrival of ruxolitinib has affected survival for these patients.

The nationwide, population-based study from the Netherlands analyzed data on more than 1900 patients with pMF comparing rates of survival from 2001 to 2010 with those from 2011 to 2018.

There was a slight increase in 5-year survival among patients from the first period to the second, rising from 51% to 55%. The biggest survival increases were seen in patients who were older than 65 years at the time of their diagnosis. Among these patients, 5-year RS increased from 38% to 45%.

Nonetheless, “[i]n accordance with previous literature, RS was markedly worse in older patients,” the authors wrote.

Higher rates of mortality were also seen in male patients and in patients who had a prior malignancy.

The study included a subgroup of 700 patients with known International Prognostic Scoring System (IPSS) scores and known treatments. Unsurprisingly, older patients had higher IPSS scores.

“In the subgroup of patients with known IPSS scores (diagnosed between 2014 and 2018), a clear association between RS and the IPSS risk category was found,” the authors wrote. “Furthermore, the multivariable analysis indicated higher excess mortality ratios both in males and in patients with a prior malignancy.”

Younger patients (<65 years) were more likely to receive early allogeneic stem cell transplantation, which increased slightly from 8% in the first period to 11% in the second. Meanwhile, use of other systemic therapy increased across all patients, rising from 3% to 14%, mainly driven by JAK1/2 inhibitors like ruxolitinib. Other systemic treatments included immunomodulatory drugs and interferon-alpha.

“The parallel increase in RS and early use of ‘other therapy’ (mainly concerning ruxolitinib) suggests effectiveness of the latter in our real-world population,” wrote the investigators. “Although the increase in the use of other therapy was similar in both age groups, the higher disease severity in patients aged >65 years might explain the greater effect size in this group. This is supported by the final overall survival analysis from the Controlled Myelofibrosis Study with Oral JAK inhibitor Treatment 1 trial.”

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<td>16.5 months vs 33 months</td>
<td>&lt;10% when treated with first- and second-generation EGFR TKIs⁴⁻⁹</td>
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*These results were not statistically significant (P=0.06). ⁴

EGFR, epidermal growth factor receptor; mNSCLC, metastatic non-small cell lung cancer; NGS, next-generation sequencing; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor.


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Gary Lyman, MD, MPH, on the Role of Health Care Institutions in Promoting Biosimilar Uptake

GARY LYMAN, MD, MPH, PROFESSOR OF CLINICAL RESEARCH, FRED HUTCHINSON CANCER RESEARCH CENTER, AND SENIOR LEAD, HEALTH CARE QUALITY AND POLICY, HUTCHINSON INSTITUTE FOR CANCER OUTCOMES RESEARCH (HICOR), FRED HUTCH, IS AN ONCOLOGIST, HEMATOLOGIST, AND PUBLIC HEALTH RESEARCHER WHO HAS LONG BEEN AN ADVOCATE FOR BIOSIMILARS. HE HAS ALSO DEVELOPED GUIDELINES IN SUPPORT OF USING BIOSIMILARS IN THE ONCOLOGY SPACE.

Do you think health care institutions need to weigh in somehow to facilitate the use of biosimilars in the clinic, and if so, how?

I think it’s a 2-way street. I think health care providers and institutions need to be fairly proactive in making their case for the use of these agents. I think payers, the providers, and the health systems need to reach out to the users to indicate what their perspective is on it. Basically, an effort to come to terms so there’s an alignment of what is encouraged by the clinical community for a particular condition and what the payer is willing to reimburse in terms of actual agents.

“...where clinicians get a little anxious about switching an agent in the middle of a course of therapy, particularly if it’s being used with curative intent. It’s not that they necessarily disagree or don’t believe the FDA regulatory process has demonstrated that these [agents] are highly similar, but they’re not exact copies.”

—Gary Lyman, MD, MPH, Fred Hutchinson Cancer Research Center

Unfortunately, those lines of communication are often frayed or nonexistent. So if a patient has been on a biologic therapy, has done well, and all of a sudden they switch insurance companies, or a payer decides to change its favored biologic, then the clinician either needs to prescribe the new favorite agent or to render a request or an appeal to be allowed to use for that patient the agent they’ve been on, for continuity.

I think that’s where clinicians get a little anxious about switching an agent in the middle of a course of therapy, particularly if it’s being used with curative intent. It’s not that they necessarily disagree or don’t believe the FDA regulatory process has demonstrated that these [agents] are highly similar [to the reference product], but they’re not exact copies. They’re not generics. Even if it’s just for a patient who’s concerned with why they’re getting a different drug than they were getting 3 weeks earlier. All this, I think raises some concerns in clinicians about switching or changing in the middle, particularly if they have not been told about it. And this is another issue that comes up about notification and approval of agents in the midst of a course of therapy for patients who are being often treated for curative intent.

I think it’s essential that those lines of communication be there and that the views and rationale from both sides are put forward. I don’t know what the final answer is. Perhaps a joint committee with representation from the payer community that holds the purse strings and a clinician or health system that does the prescribing and is basically trying to serve the interests of the patient. Of course, the patient is left in the middle of all this and is not quite sure what’s going on. I think we really need to find a way for more routine regular and patient-centered alignment of the interests of both the payer and the provider for the best interest of the patient.

Could you briefly explain how biosimilar uptake in the oncology space differs from that in other spaces, such as rheumatology?

As an oncologist, of course I’m most familiar with the agents approved and utilized within oncology, within cancer treatment and supportive care. I’m certainly not appraised of all the indications and uptake of agents used outside the oncology space. I know that in rheumatology and selected other areas that biologics have had a major impact on patient care and treatment and outcomes, and I would anticipate they will be as aggressively evaluated and taken up as in oncology.

The majority of FDA-approved biosimilars are in the oncology space. I think, when I last looked, 17 of the 29 approved biosimilars are drugs that we use routinely in oncology, either for supportive care—like hematopoietic growth factors—or for actual cancer treatment. So they’ve had a dramatic impact in oncology, including the very first biosimilars approved in the United States were supportive care biosimilars for oncology.

Biologics have impacted dramatically across medical disciplines in many areas. As the patents expire on these agents, all of which have increased substantially in price since their original approval, and this can often limit access or willingness to utilize. I think there’s no question that the introduction of biosimilars is having a fairly substantial effect across disciplines.

I can speak to oncology, again, that guidelines made from major professional organizations including ASCO (American Society of Clinical Oncology), the NCCN (National Comprehensive Cancer Network), and Europe, as well, have embraced biosimilars. In fact, in a forthcoming updated policy statement from ASCO, they reiterate their policy and position that biosimilars are equally valuable options to originators when they’re approved by the FDA for use in oncology.

So, not a direct answer to your question, because I don’t have a lot of data outside of oncology, but I see no differences in the regulatory process in safety and efficacy concerns. Perhaps in oncology, my biased perspective is that the diseases that we manage are often life-threatening and more serious. This both raises the importance of providing access to these expensive therapies, but could raise concerns from a clinical perspective that if there was any compromise of the efficacy of a biosimilar, there could be impacts on patient outcomes, longevity, survival. But we’ve seen none of that with the anticancer biosimilars. While they’re more recent, generally approved the last 2 or 3 years they’ve been approved, it appears that they’re being integrated into oncology guidelines and utilized in practice fairly routinely and increasingly.
Todd Schlesinger, MD, FAAD: Surgical Decisions for Skin Cancer Are Multimodal

The characteristics of the tumor and the presence of surgical fatigue can help determine patients’ candidacy for skin cancer surgery, Schlesinger explained.

Why might patients with skin cancer not be candidates for surgery, and what are some of the functional incapacity risks for those who are? Assessing risk for surgical intervention for skin cancer, nonmelanoma skin cancer, is a multimodal consideration. One of the main considerations that you might think of if you’re deciding whether a patient will or will not be a candidate for surgery might be location of the tumor. If a tumor happens to be located near a large structure—the eye, the ear, the nose—or the surgery may result in significantly more morbidity for the patient, such as removal of an eye or a large part of the ear of the nose, other considerations may come to mind as well. Or if it’s a particularly very large tumor, some tumors are just not surgical candidates. You may be presented with a very large, advanced skin cancer covering half the back or maybe in the genital area that just isn’t a good candidate.

There are other patients who may present who may be considered a nonsurgical candidate: They have just a lot of tumors, surgical fatigue, or just the tiredness of having multiple surgeries over time can also be another factor to consider. There are several things to think about—the subtype and aggressiveness of the tumor being dealt with is a consideration. Whether the tumor has been treated before with radiation or prior surgery, whether it’s recurrent or not, these are all things that we think about when it comes to surgery.

And then we also have patients who are just of advanced age, and they may not desire to have another surgical procedure and they also may have the option of using one of these medical therapies. So, it’s a multimodal consideration that we have to think of as dermatologists.

Ivo Abraham, PhD, RN, on How Neulasta Onpro Is Having an Impact on the Biosimilars Space

IVO ABRAHAM, PHD, RN, A PROFESSOR IN THE DEPARTMENT OF PHARMACY PRACTICE AT UNIVERSITY OF ARIZONA HEALTH SCIENCES, DISCUSSES THE CURRENT STATE OF THE GRANULOCYTE COLONY-STIMULATING FACTOR (G-CSF) SECTOR OF THE BIOSIMILAR MARKET. ABRAHAM IS ALSO A HEALTH CARE CONSULTANT AND COFOUNDER AT MATRIX45.

You recently published 2 cost-efficiency analyses showing the potential savings that could be generated by switching patients from Neulasta Onpro [pegfilgrastim] to a biosimilar pegfilgrastim. Could you briefly explain these findings and how they can help inform prescribing decisions?

Well, we started doing these studies over 10 years ago, and we’re doing them in Europe. We were trying to show that yes, savings should be achieved. That’s not rocket science. If something is priced lower than another product, obviously, you’re going to achieve some efficiencies. But then we also started looking at how can the savings that have been generated be applied to purchase more treatments on a budget-neutral basis. So, let’s say, you save a million dollars. Now, you could put that million dollars back into your general account. As a payer, you can either give prophylactics to more patients, [like] G-CSF drugs that prevent febrile neutropenia [FN] and neutropenia generally, or purchase more of the newer cancer treatments.

So we have done all of these comparisons now. Amgen, and for disclosure reasons I’ll say we’ve done work for Amgen over the years, had an ingenious idea with Neulasta Onpro, because it protects the pegfilgrastim franchise that they have, obviously, but it also has a convenience factor. Patients do not have to come back the next day to get this 1 shot of pegfilgrastim. After you apply it, about 27 to 28 hours later, [the Onpro device] administers [the drug]. You don’t have to come back for your prophylactics.

Now, one concern that started popping up in the literature and in the cancer community is that it’s a device, and devices occasionally fail. There have been reports of between 1.9% and 6.7% of devices are failing. The consequence of that is that suddenly a patient who [should be] receiving a prophylactic and knows that they have a highly myelotoxic chemotherapy regimen may no longer be getting the prophylactic. That triggers a whole cascade. If they are not receiving that prophylactic and are at risk for FN, they now are at a higher risk of FN, which may lead in turn to hospitalization.

A large proportion, probably the majority of FN cases, especially with older patients or patients with very advanced cancer and have very toxic chemotherapy regimens, will end up being hospitalized. The cost estimate of hospitalization in today’s terms is probably somewhere between $30,000 and $35,000. So, suddenly, as a payer, you have to add another $35,000 to managing this particular patient.

Now, there is an alarm function on the device in case it malfunctions but [concerns] remain. Patients may have been educated about the risks of the device failure, but imagine being a patient with cancer. There’s only so much you can hear on the day of chemotherapy. So here the first time they’re applying it and the nurse or pharmacist may tell you, “There is something in it if it goes bad, but still, it may happen.” So, we need to take into account the risks and the additional costs because if you have to pay more as a payer, there’s going to be less money for something else.

“So we’re going to see more stage III and stage IV cancers. Now, on the other hand, these are also some of the cancers where in the last 15 to 20 years, we have made enormous progress.”

—Ivo Abraham, PhD, RN, University of Arizona Health Sciences

A lot has been said about the health care system now having to recoup costs after the outlays for coping with the pandemic. Where do you think this might lead?

The [COVID-19] pandemic has been good for biosimilars because we’ve all been trying to figure out how to deal with the pandemic and how to reduce costs, in general, but also with the additional outlay that payers are experiencing with regard to covered lives who end up developing COVID-19. So, there is, in general for generics and biosimilars, a very strong reason to be continued. Also, we’ve built confidence. What it has shown us is that despite the fear mongering that we saw a few years ago, and that we saw 10 years ago in Europe—fear mongering about how these [biosimilar] products are never the same as the [reference] product or the biosimilar product is not the same from batch to batch—we’re beyond that. COVID-19 certainly helped with that.

Another element to consider in this is that COVID-19 helped us with telehealth. Now, suddenly, CMS was beginning to reimburse for telehealth, which CMS resisted for a long time because of many reasons. We’re going to probably see how especially provider organizations are going to deal with the costs,
which is then going to go to the payers as procedures get picked up again and [providers] do more imaging. Basically, the things that are high-ticket items that can help them recoup costs.

The reality about biosimilars is despite a slow update in the United States, it has to do with the biosimilar companies thinking that they had to do door-to-door selling. They’ve got to go to meet with big name and second- and third-tier big name companies to educate them about biosimilars. That was until they realized that’s not the business model. The business model is to get big contracts. The United States should have learned that from Europe.

So, from that point of view, I think the good thing, and also facilitated by COVID-19, is that now we realize biosimilars, certainly the ones in the United States, are just as good as the reference products and we don’t have to worry about safety. Moreover, as a prescriber, we may have no choice [with] what product we’re working with.

As patients flock back to their doctors, many will be seeking treatment for later stage cancer than had the pandemic not occurred. Can you comment on this trend and what it signifies?

As the surgeons are saying, the tumors are larger. Patients have been postponing screenings because of the pandemic. They may have been ignoring or trying to ignore certain symptoms. We also need to take into account that, in general and pre-pandemic, patients don’t like to acknowledge that something might be wrong. I always say, if it’s not right in the belly or it’s below the waistline, men and women are very reluctant to admit that there might be a problem. Men with prostate cancer; women with some of the gynecological cancers; both genders with colorectal cancer. So that’s where COVID-19 no doubt has had a very bad effect.

I think we’re going to see it in the statistics when they come out a year from now from cancer centers and what cancer.gov puts out every year. We’re going to see more stage III and stage IV cancers. Now, on the other hand, these are also some of the cancers where in the last 15 to 20 years, we have made enormous progress. It’s not that a patient with stage 4 colorectal cancer has been looking for a cure. This is not that a patient with colorectal cancer has very limited prospects.

Now, they have a few more prospects. There’s a certain tinge of hope, there’s enormous progress. It’s not that a patient with stage 4 colorectal cancer has a very limited prospects. Now, they have a few more prospects. There’s a certain buffer in that regard, but the reality is still that we were trying to be wise. I probably would have done the same thing and said, “[Screenings] can wait and this COVID-19 thing is going to be over in a few months,” or something like that. And, yeah, the surgeons are saying the tumors are bigger.

Do physicians think it controversial to allow pharmacists to switch out reference products with biosimilars?

I don’t view this as a controversial move, because these decisions really are not made in silos. So, particularly in health system settings, there are often agreed-upon pharmacist-led initiatives approved through P&T committees that can ultimately provide the pharmacy team the authority to make certain substitutions and drive formulary adherence. This allows for greater efficiencies with the product review process, and given the nature of biosimilars and more of them coming to market, it can really help streamline the operations while making clinically sound and cost-effective formulary decisions.

So, you’re right. We’ve seen these strategies implemented, where biosimilars have been defined to fall under the purview of pharmacists’ authority for formulary decisions and so decisions become more of an informational item in P&T committee meetings vs an action item. But it’s important to note that the practice of using therapeutic interchanges is common in health systems. Therapeutic interchanges, or TIs, are essentially authorized exchanges of therapeutic alternatives in accordance with previously established and approved guidelines, policies, or protocols within a formulary system. So, these TIs are used with drug products that may even have different chemical structures but are expected to have the same therapeutic effects and safety profiles when administered to patients. This concept as a whole is really not new and it’s been in existence for some time, particularly in the health system setting.

But again, these are agreed-upon evidence-based initiatives driven through the formulary management process that are aimed at streamlining and standardizing treatment options. I’ll add that there are policies and steps and processes in place, too, that if a provider seeks to order a nonformulary product, for example, that is available as well, which may elicit some additional steps.

Do physicians’ concerns about biosimilars differ from those of pharmacists?

We probably can’t generalize the similarities or differences with concerns with biosimilars. What we could do is look at it from a different lens to try to understand what considerations may be more prevalent for each stakeholder type. For example, given the premise of biosimilars, in that they have clinically no meaningful differences and expected to have the same outcomes, there could be a bias from a provider perspective to continue utilizing the treatment they’re most familiar with. So, there’s an element of “why switch?” which has really been overcome by the financial assessments that show economic benefits that can be realized by the patient and the organization. But that could be concern that’s more top-of-mind from a provider perspective.

Now, from a pharmacist perspective, in addition to clinical considerations, given the role they play within their organizations in evaluating products for formulary addition, for example, there’s more exposure to the financial and operational components of biosimilars as well. Challenges can include conducting payer coverage assessments and the inventory management implications of varying payer policies, which can result in carrying some biosimilars, all biosimilars, and the originator biologic at times.

Additionally, there’s an IT [information technology] component in which the pharmacy and P&T [pharmacy and therapeutics] committee must ensure the appropriate EHR [electronic health record] system updates are made to the preferred drug list, data or order sets, and ensure the right products are procured, administered, and billed accurately. So, there’s some additional considerations, outside the clinical component, that may be more top-of-mind for pharmacists as well.

Is there a solution to the cost and complexity that health care clinics face in having to stock multiple biosimilars to meet diverse payer policy requirements?

It is definitely a significant challenge, and there’s not really a one-size-fits-all solution to this, unfortunately. Depending on the facility size, patient volume, and, most significantly, the payer mix naturally in their policies, different approaches to the procurement process and inventory management may be necessary. For example, we’ve seen clinics limit their inventory for these outpatient infusions biosimilars to just a couple days’ supply or a couple of weeks’ supply to be reflective of the patients’ schedules in that time period.

So, strategy such as just-in-time ordering from a distribution standpoint to enable that quick turnaround time needed to meet the needs. Another example of strategy is obtaining prior authorizations as part of the workflow prior to purchasing or procurement the products. This is to ensure the right product is available to be administered to the patient and that it will be reimbursed. This continues to be a challenge, especially as we get more and more products entering the market for the same existing biologics, and it continues to be top-of-mind as a key challenge with adopting biosimilars.
TRIPLE-NEGATIVE BREAST CANCER: TURNING A NEGATIVE INTO A POSITIVE

PTCE would like to acknowledge Merck Sharp & Dohme Corp for their generous support of pharmacist education.

CHARACTERIZED BY THE ABSENCE OF MARKERS, metastatic triple-negative breast cancer (mTNBC) historically has a poor prognosis. Multiple new options in TNBC and conflicting data are a challenge for payers to manage. As part of a virtual satellite symposium during AMCP e-Learning Days, 3 expert speakers, Allison Schepers, PharmD, BCOP; Brandy Strickland Snyder, PharmD, BCOP, MBA; and Laura R. Bobolts, PharmD, BCOP, as moderator, delved into the clinical data and impact on health care use in a panel discussion titled Immuno-oncology Therapy for Metastatic Triple-Negative Breast Cancer: Emerging Clinical Data and Payor Considerations.

Laura Bobolts, PharmD, BCOP, posed, “Challenges to managing costs specific to metastatic TNBC include FDA indications that are broader than the scientific evidence, enforcing sequencing when the optimal sequence is unknown, and the design of the clinical trials with regard to the overall survival end point.”

Schepers led with a discussion on the efficacy of the combination of immune checkpoint inhibitors (ICIs) with chemotherapy, noting neither multiagent chemotherapy nor single-agent ICIs are markedly effective in TNBC. Multiple chemotherapy-immunotherapy regimens have demonstrated efficacy and are available for mTNBC including as follows:

- Atezolizumab and nab-paclitaxel in patients with PD-L1 positivity greater than or equal to 1% of tumor-infiltrating immune cells
- Pembrolizumab and chemotherapy in patients with PD-L1 positivity greater than or equal to 10 combined positive score
- Pembrolizumab after progression on prior treatment for patients with microsatellite instability high/deficient mismatch repair or a high tumors mutational burden

The panelists highlighted the controversy surrounding atezolizumab and nab-paclitaxel, given the original study (Impassion130) had positive long-term follow-up results; however, the confirmatory trial (Impassion131) did not show an improvement in progression-free survival. Nonetheless, the Oncologic Drugs Advisory Committee voted for continued approval of atezolizumab and nab-paclitaxel for the treatment of patients with advanced or mTNBC whose tumors are positive for PD-L1 expression. They also discussed the potential for use of ICIs in patients with early-stage disease, potentially impacting results of ICIs in mTNBC.

Bobolts started by reviewing top payer challenges associated with anticancer agents. She then summarized the traditional methods of managing drug application costs before providing some additional tailored managed care strategies including:

1. Oncology clinical pathways
2. Site-of-care steerage
3. Value-based care programs
4. Bundled payments
5. Restructured provider networks

Bobolts emphasized the average cost of treatment of mTNBC ranges from $21,908 to $25,845 per month. She presented a recent study of patients with TNBC in the California Cancer Registry that found that the majority of patients who did not receive National Comprehensive Cancer Network (NCCN) guideline concordant care and NCCN discordant care were associated with an increase in disease-specific mortality. Another study found patient costs were nearly $2000 higher for the roughly 18% of patients with metastatic breast cancer receiving NCCN guideline discordant care.

Snyder then focused the discussion on the use of alternative payment models in oncology and shared results from the Centers for Medicare & Medicaid Services (CMS) Oncology Care Model. She transitioned to the proposed CMS Oncology Care First Model, and then highlighted pharmacists’ roles in providing cost-effective care by optimizing treatment to improve patient efficacy and safety outcomes while managing costs.

The panel then reconvened to discuss the impact of alternative payment models to their practices and patient care as well as their roles within the oncology team to meet goals of value-based care. They highlighted challenges with staying abreast of changes in labeling when accelerated approval transitions to full approval, as well as formulary considerations and implementation strategies.

To view the on-demand CE session, please visit WWW.PHARMACYTIMES.ORG/GO/MTNBC.

The activity is available through December 29, 2021.

LOWERING COST OF CANCER CARE THROUGH BIOSIMILARS

PTCE would like to acknowledge Amgen Inc and Coherus Biosciences for their generous support of pharmacist education.

A TRIO OF EXPERTS, Scott A. Soefje, PharmD, MBA, BCOP, FCCP, FHOPA; Ashley E. Glode, PharmD, BCOP; and Yuyuan Liu, PharmD, convened to review the unique combination of clinical, economic, and policy factors impacting biosimilar adoption in a presentation titled Oncology Biosimilars: The Value to Managed Care as part of a virtual satellite symposium and panel discussion during AMCP eLearning Days.

Scott A. Soefje, PharmD, MBA, BCOP, FCCP, FHOPA, explained, “ Savings enabled by the presence of biosimilars are modeled to exceed $100 billion in aggregate over the next 5 years, though volume and price dynamics remain volatile and significant uncertainty remains.”

Soefje moderated the session and kicked off the program by illustrating 29 biosimilar products currently approved by the FDA. He offered the Purple Book as the most up-to-date source of information on biosimilar approvals. He explained that while total spending in oncology is on the rise, the adoption of biosimilars has potential to spur reduced biologic expenditures through competition. Soefje highlighted the high uptake of the 3 biosimilars launched in 2019, bevacizumab, trastuzumab, and rituximab, and the associated average selling price reductions of $500 to $1900 for a standard course of treatment. The panelists then shared perspectives on biosimilar considerations for patient care, clinical pharmacy practice, and managed care.

Glode tackled some of the challenges with adoption of biosimilars including the perception that they are less effective, the potential for unintended immune responses and immunogenicity, and the logistical barriers at the individual patient level. Glode focused on implications of extrapolation of data from one indication to all approved indications, noting this is a core tenet of biosimilarity. She then reviewed the process for formulary considerations for biosimilars, citing the biggest challenge is the frequent changes in payer
T-cell therapy is a core treatment asset in Pharmaceutical Corporation for their generous support of pharmacist education. CE would like to acknowledge Bristol Myers Squibb, Kite Pharma, Inc., and Novartis PT.

AN EXPENSIVE “CAR T”

To wrap up the panel, the speakers discussed processes for assessment and adoption of a new biosimilar. They speculated on the ideal payment model for oncology biosimilars and the potential impact of immune checkpoint inhibitor biosimilars in the future.

To view the on-demand CE session, please visit WWW.PHARMACYTIMES.ORG/GO/BIOSIMILARS.

The activity is available through December 29, 2021.

STRATEGIES TO LIGHTEN THE LOAD OF AN EXPENSIVE “CAR T”

P/TEC would like to acknowledge Bristol Myers Squibb, Kite Pharma, Inc., and Novartis Pharmaceuticals Corporation for their generous support of pharmacist education.

CHIMERIC ANTIGEN RECEPTOR (CAR) T-cell therapy is a core treatment asset in multiple hematologic malignancies, including acute lymphoblastic leukemia, multiple myeloma, diffuse large B-cell lymphoma, mantle cell lymphoma, and follicular lymphoma. The acquisition costs of CAR T-cell therapies range between approximately $370,000 and $475,000; therefore, understanding how to optimize both costs and outcomes is key for managed care professionals. In a live virtual broadcast at the 2021 AMCP Annual Virtual Meeting, an expert panel of speakers moderated by Anthony Perissinotti, PharmD, BCOP, offered solutions in a presentation titled An Expert Panel Discussion on CAR T-Cell Therapy: The Costs, Value, and Strategies to Improve Access.

Zahra Mahmoudjafari, PharmD, BCOP, kicked off the session with a concise review of safety and efficacy for the 5 CAR T-cell products currently FDA approved: axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel, tisagenlecleucel, and, most recently, idecabtagene vicleucel. Dr Mahmoudjafari then went over monitoring and management strategies for key toxicities associated with CAR T-cell therapy, including cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, delayed cytopenias, and hypogammaglobulinemia.

In the final portion, Rebecca Borgert, PharmD, BCOP, reviewed available data relating to cost-effectiveness of CAR T-cell therapy citing quality-adjusted life-years (QALYs) ranging from $37,000 to $223,000/QALY. She explained that the type of payer and CAR T-cell infusion setting influence payment path. Borgert highlighted that the current reimbursement model results in substantial losses for health care centers in Medicare beneficiaries and, in general, will not be sustainable as CAR T-cell therapy indications expand. Numerous alternative payment and care delivery models have been developed and could be applied to CAR T-cell therapy, including as follows:

• Outcome-based pricing arrangements
• Centers of Excellence networks
• Bundled payments
• Credit mechanisms
• Cost-sharing
• Managed entry agreements
• Milestone-based contracts

Borgert wrapped up the session by reviewing barriers and potential solutions to patient access associated with CAR T-cell therapy.

To view the on-demand CE session, please visit WWW.PHARMACYTIMES.ORG/GO/CAR-T-STRTG.

The activity is available through April 26, 2022.

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Health Insurance, Blood Cancer Care, and Outcomes: A Literature Review

KAREN CROTTY, PHD, MPH; MARIALANNA LEE, MSC; KATHERINE TREIMAN, PHD; MARIA SAE-HAU, PHD; CANDI WINES, MPH; CATHERINE VIATOR, MS; AND ELISA WEISS, PHD

Continued from cover

In light of these challenges, there is an urgent need to identify insurance reforms that can meaningfully improve access to affordable, high-quality care for patients with blood cancer. To assess the current evidence base for such reforms, we conducted a literature review and gap analysis. Our aims were, first, to identify and categorize current evidence regarding the impact of health insurance status and type on access to care and outcomes among patients with blood cancer, and second, to identify areas of uncertainty and key research gaps.

Methods
We conducted a systematic search of Medline's PubMed database on June 5, 2020, and an additional targeted author search on July 1, 2020. Search terms included relevant Medical Subject Headings as well as relevant blood cancer and insurance keywords. Search terms were identified by reviewing key terms in recent insurance and blood cancer publications and were developed in collaboration with experts and in consultation with an information scientist. The search was supplemented by reviewing the bibliographies of any identified review articles. The combined searches yielded 1101 articles. To identify the subset of relevant publications that would inform policymakers and the scientific field of the insurance research landscape related to blood cancer care and outcomes, we screened titles and abstracts for eligibility against a set of inclusion and exclusion criteria. Studies were eligible for inclusion if they involved patients with blood cancer at any stage on the cancer care continuum and had a focus on insurance. We included studies with insurance as the primary focus of the study and studies in which insurance was a variable or an outcome of the study. All study designs were eligible, including review articles and qualitative research. We excluded studies specifically focused on cancers other than blood cancer but included general cancer studies if they were known to or very likely to include patients with blood cancer. We excluded studies published before January 2000, those conducted outside of the United States (or its territories), and those not in the English language. We also excluded animal and in vitro studies, letters to the editor, and publication comments.

To provide an overview of the available scientific literature and a gap analysis to identify areas of uncertainty and research that are missing or underrepresented, we categorized included articles using the population, intervention, comparator, and outcomes framework to structure data abstraction. Given the scope and purpose of the review, categorization was based on a review of abstracts by a single research analyst and quality checked by a senior methodologist. We did not conduct a risk-of-bias assessment, and we retrieved full texts only for studies that did not include an abstract or when relevant information was not presented in the abstract. Abstracted categories included study title, author, publication year, sample size, study design, cancer focus, population group, insurance type, cancer continuum, comparator, and outcome. For each category, we established predefined coding variables and abstracted the main insurance-related outcome finding into a free-text field. The categorization process was primarily conducted on the information available in the study abstract.

Results
Overview of the Research Landscape
Following title and abstract review, we identified 154 publications for inclusion, 70 of which had a direct focus on insurance as the subject of the article; of those, 39 focused specifically on blood cancers. Studies were predominantly large retrospective cohort studies often using Medicare claims data or the National Cancer Institute-funded Surveillance, Epidemiology, and End Results (SEER) registry data or SEER-Medicare data as the basis for analysis. Almost half of the retrospective studies focused on the association between insurance status or type and an outcome of interest. The remainder reported insurance as one of several factors found to be associated with a clinical outcome (eg, survival), quality of cancer care, or access to treatment. One prospective cohort study assessed the quality of cancer care for older patients provided by the Veterans Health Administration vs fee-for-service Medicare. Of 2 identified systematic reviews, one 2005 study was specific to blood cancer and found (from very limited quality-of-life [QOL] data) that individuals with chronic lymphocytic leukemia experience challenges obtaining health insurance. The other was a recent 2020 systematic review that investigated evidence related to health insurance coverage disruptions and cancer outcomes and found that those patients with coverage disruption were more likely to have advanced disease, be less likely to receive treatment, and have worse survival than their counterparts without coverage disruptions.

More than half of the identified studies addressed multiple types of insurance, and Medicare was the focus of 16% of studies. Medicaid was rarely studied as the sole focus of a study. Studies with a focus on adults (65 years and younger) were most common, addressed in one-third of all included studies, followed by adolescents and young adults (addressed in 21% of studies) and older adults (addressed in 19%). Children were a focus of just 9% of included studies, and a handful of studies were not focused on any patient population but rather on physician opinion or practices. Of the 39 studies specific to blood cancer and insurance, none specifically focused on diverse racial and ethnic groups or patients in rural settings.

Studies tended to focus on patients in active treatment, addressed by 42% of all included studies. Survivorship was also commonly studied, addressed in almost a quarter of studies. Notably, just 2 studies addressed treatment in the context of clinical trial participation, one of which specifically focused on patients with blood cancer. A 2014 case study by Preussler and colleagues highlighted state variation in Medicaid coverage of complex oncology treatments for blood cancer and found that only a few states provided the recommended benefits (ie, benefits recommendations developed by multiple stakeholders) for hematopoietic cell transplantation clinical trial coverage.

Mortality/survival and access to care were among the outcomes most often studied, addressed in 35% and 33% of the 154 studies included, respectively. Studies addressing access to care were broad and included the impact of insurance status and type on receipt of or timeliness of treatment.

Key Insurance-Related Findings and Gaps Specific to Blood Cancer Insurance and survival
Fifty-six percent of studies that focused specifically on blood cancer and...
Table 1: Overview of 21 Retrospective Cohort Studies Examining the Impact of Insurance Status or Type on Survival.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Sample size</th>
<th>Population</th>
<th>Insurance comparison</th>
<th>Survival outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cancer studies reporting disparities in survival based on insurance status or type</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Colton et al, 2019</td>
<td>66,556</td>
<td>Adolescents and young adults with lymphoma or leukemia</td>
<td>Private insurance vs public or no insurance</td>
<td>Favors private insurance</td>
</tr>
<tr>
<td>Olszewski et al, 2018</td>
<td>9755</td>
<td>Medicare Part D beneficiaries or patients with other creditable prescription drug coverage with myeloma</td>
<td>Prescription drug coverage vs no prescription drug coverage</td>
<td>Favors prescription drug coverage</td>
</tr>
<tr>
<td>Goldstein et al, 2018</td>
<td>43,648</td>
<td>Patients 65 years and younger with NHL</td>
<td>Private insurance vs no insurance</td>
<td>Favors private insurance</td>
</tr>
<tr>
<td>Tang et al, 2019</td>
<td>11,861</td>
<td>Patients with cutaneous T-cell lymphoma</td>
<td>Private insurance vs no insurance, Medicare, or Medicaid</td>
<td>Favors private insurance</td>
</tr>
<tr>
<td>Pulit et al, 2017</td>
<td>10,690</td>
<td>Patients with AML</td>
<td>No insurance and Medicaid vs other insurance</td>
<td>Favors other insurance</td>
</tr>
<tr>
<td>Perry et al, 2017</td>
<td>5784</td>
<td>Patients 65 years and younger with CML</td>
<td>Medicaid vs other insurance</td>
<td>Favors other insurance</td>
</tr>
<tr>
<td>Ortiz-Ontiz et al, 2014</td>
<td>516</td>
<td>Patients in Puerto Rico with leukemia ( unspecified)</td>
<td>Government health plan vs nongovernment health plan</td>
<td>Favors nongovernment health plan</td>
</tr>
<tr>
<td>Fintel et al, 2015</td>
<td>10,403</td>
<td>Adolescents and young adults with acute lymphoblastic leukemia</td>
<td>Insurance vs no insurance</td>
<td>Favors insurance</td>
</tr>
<tr>
<td>Master et al, 2016</td>
<td>67,443</td>
<td>Adults with AML</td>
<td>Private insurance vs Medicaid, Medicare no insurance, or unknown insurance status</td>
<td>Favors private insurance</td>
</tr>
<tr>
<td>Selby et al, 2001</td>
<td>59</td>
<td>Related-donor hematopoietic stem cell transplantation patients with AML or CML</td>
<td>Insurance vs no insurance</td>
<td>Favors insurance</td>
</tr>
<tr>
<td>Pulit et al, 2015</td>
<td>37,253</td>
<td>Patients with NHL</td>
<td>Non-Medicaid insurance vs Medicaid or no insurance</td>
<td>Favors non-Medicaid insurance</td>
</tr>
<tr>
<td>Costa et al, 2016</td>
<td>10,161</td>
<td>Patients younger than 65 years with multiple myeloma</td>
<td>Uninsured or Medicaid vs other insurance</td>
<td>Favors other insurance</td>
</tr>
<tr>
<td>Keegan et al, 2016</td>
<td>9353</td>
<td>Adolescents and young adults with Hodgkin lymphoma</td>
<td>Private or military insurance vs public health insurance or no insurance</td>
<td>Favors private or military insurance</td>
</tr>
<tr>
<td>Har et al, 2014</td>
<td>3858</td>
<td>Adults with DLBCL</td>
<td>Private insurance vs no insurance or Medicaid</td>
<td>Favors private insurance</td>
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<tr>
<td>Goldstein et al, 2019</td>
<td>NR</td>
<td>Adults with Burkitt lymphoma</td>
<td>Private insurance vs nonprivate insurance</td>
<td>Favors private insurance</td>
</tr>
<tr>
<td>Parikh et al, 2015</td>
<td>45,777</td>
<td>Adults with Hodgkin lymphoma</td>
<td>Private insurance vs no insurance or Medicaid</td>
<td>Favors private insurance</td>
</tr>
<tr>
<td>Bradley et al, 2011</td>
<td>523</td>
<td>Patients with AML</td>
<td>Private insurance vs nonprivate insurance</td>
<td>Favors private insurance</td>
</tr>
</tbody>
</table>

Blood cancer studies reporting no difference in survival based on insurance type

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Sample size</th>
<th>Population</th>
<th>Insurance comparison</th>
<th>Survival outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Srour et al, 2017</td>
<td>217</td>
<td>Adults with AML</td>
<td>Publicly insured vs privately insured vs no insurance</td>
<td>No difference</td>
</tr>
<tr>
<td>Al-Amer et al, 2014</td>
<td>130</td>
<td>Adults with AML</td>
<td>Regression model using any insurance type</td>
<td>No difference</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Sample size</th>
<th>Population</th>
<th>Insurance comparison</th>
<th>Survival outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yung et al, 2016</td>
<td>2073</td>
<td>Nonelderly adults aged 21-64 years with AML or Hodgkin lymphoma</td>
<td>Medicaid enrolled vs nonenrolled</td>
<td>Mixed findings</td>
</tr>
<tr>
<td>Olszewski and Foran, 2015</td>
<td>5797</td>
<td>Patients with DLBCL</td>
<td>Factors mediating insurance-associated survival disparities</td>
<td>Mixed findings</td>
</tr>
</tbody>
</table>

Table continues...

- **AML**: acute myeloid leukemia
- **CML**: chronic myeloid leukemia
- **DLBCL**: diffuse large B-cell lymphoma
- **NHL**: non-Hodgkin lymphoma
- **NR**: not reported

insurance (22 of 39) reported survival as an outcome of interest. Of these, 21 examined the impact of insurance status or type on survival (Table). Seventeen studies found disparities in overall survival (OS) based on insurance status and type, and 2 reported no difference in OS based on insurance type. All but one study reporting survival disparities were large retrospective registry studies, and overwhelmingly, they reported better survival among patients with insurance compared with those with no insurance and better survival among patients with private commercial insurance compared with other insurance types. In contrast, the 2 studies reporting no difference in OS based on insurance type were small chart reviews.

Of the 2 studies reporting mixed survival outcomes, both were large registry database studies. One found increased OS among Medicaid-enrolled beneficiaries compared with non-Medicaid-enrolled beneficiaries (with the non-Medicaid group including both commercially insured and uninsured patients) with acute myeloid leukemia and Hodgkin lymphoma enrolled in New York State; however, there was no such difference in survival among Medicaid beneficiaries enrolled in California. In a 2015 study, Olszewski and Foran found that when confounding factors are considered, insurance-associated lymphoma survival disparities are partly mediated by the prevalence of known prognostic factors or by patients’ preexisting medical conditions that at the time drove eligibility for Medicaid and Medicare; these authors noted that cancer registries generally do not contain information about comorbidities or other confounders.

One study assessed the timeliness of care (defined as time from payer approval to actual HCT) and its impact on OS for patients who underwent hematopoietic cell transplantation (HCT). Total time to HCT was longer for patients insured by public payers than for those with private insurance (median, 66 days [range, 14-277] vs 48 days [range, 1-407]; P < .001), but timeliness was not associated with OS. Insurance and financial burden. Thirteen of 39 studies that focused specifically on blood cancer included financial burden as an outcome of interest. Overall, the findings point to a significant insurance-related financial burden for patients with blood cancer. Notably, most studies addressed financial burden among Medicare beneficiaries, whereas few studies investigated the size and impact of the financial burden placed on uninsured patients and Medicaid beneficiaries with blood cancer. Of 13 studies, 8 focused on Medicare Part D. Of these, 5 reported increased financial burden on patients related specifically to high cost-sharing under Medicare Part D, which also reported that high cost-sharing under Medicare Part D was associated with reduced or delayed initiation of specialty drugs (ie, tyrosine kinase inhibitors [TKIs]). The second reported a substantial financial barrier to accessing orally administered anticancer therapy for those not receiving low-income subsidies. The third study focused on those receiving Medicare Part D benefits who did not receive low-income subsidies, those patients who were heavily or moderately

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subsidized demonstrated greater nonadherence to TKI treatment.44 This study demonstrated an association between low-income subsidies and nonadherence but did not claim that low-income subsidies cause nonadherence.45 Unrelated to Medicare Part D, a small study found that among 20 US cancer center directors and chief medical officers surveyed, 15 were concerned about the financial viability of their chimeric antigen receptor T-cell immunotherapy programs, citing Medicare reimbursement rates and manufacturer prices as the primary drivers of viability concerns.46

Two studies reported financial burden for those with commercial health insurance. A 2014 study reported on the financial burden associated with higher copayments,47 and a 2001 (pre-ACA) study reported that 61% of survey respondents paid out of pocket for some aspect of medical care that was not covered by their health insurance coverage following a diagnosis of hairy cell leukemia.48 Just one study from 2015 reported on the financial burden for Medicaid beneficiaries with blood cancer,49 and a 2011 study reported on the costs of inpatient treatment for uninsured patients with acute myeloid leukemia.50

Access to insurance. A few studies analyzing pre-ACA data highlighted the difficulty in obtaining health insurance (or in navigating gaps in insurance) following a blood cancer diagnosis.51-53 Expanding access to comprehensive health insurance coverage was a primary mission of the ACA,5 and now, post ACA, a blood cancer diagnosis is no longer the threat it once was to a patient’s ability to enroll and stay enrolled in a health plan. Although multiple studies have examined the impact of the ACA on insurance coverage and insurance-related outcomes pre- and post implementation, only one pre-ACA study was found to have focused on a population of patients with blood cancer. In a 2019 registry study, Ramachandran and colleagues observed no difference in the rates of newly diagnosed cutaneous T-cell lymphoma by insurance type (defined as uninsured, Medicaid insured, and non-Medicaid insured) before and after full implementation of the ACA.52 This was true when looking across all states, whether Medicaid expansion or nonexpansion states.52 Also related to access, one study found that lack of insurance was associated with advanced stage of Hodgkin lymphoma diagnosis.53

Insurance and clinical trial access. Only one study looked at insurance-related access to clinical trial participation for patients with blood cancer. A 2014 case study investigating the variation in Medicaid policies among states in 2012 found that only a few states provided the recommended benefits (ie, recommended benefits developed by multiple stakeholders) for hematopoietic cell transplantation clinical trial coverage.54

Insurance and race/ethnicity. A number of studies reported an association between race/ethnicity and blood cancer outcomes, with poorer outcomes for patients who are Hispanic. African American and non-Hispanic Black.55-57 However, just 2 examined whether race/ethnicity remained associated with varying outcomes after adjusting for insurance status.56,57 and both found that race/ethnicity was no longer significantly associated with blood cancer outcomes when regression models were adjusted for insurance status.

**Insurance and other outcomes.** Only a handful of blood cancer–specific studies addressed quality of care58-61 or health-related QOL (HRQOL)62 as outcomes of interest, and these were not primary outcomes of any of the identified studies. The relationship between these outcomes and insurance status among patients with blood cancer remains largely unknown.

**Discussion/Gaps in the Current Evidence** That a modest body of scientific evidence suggests that survival among patients with blood cancer is affected by insurance status and type, with better OS among the insured vs the uninsured and better OS among those with commercial insurance vs public insurance. Similarly, studies of registry and claims data suggest a significant insurance-related financial burden for patients with blood cancer. However, a number of limitations are associated with the existing literature, which ultimately hinder the development of evidence-based policymaking in this area. Evidence of the associations among insurance status, insurance type, survival, and financial burden are based primarily on retrospective cohort studies that may fail to control for comorbidities and confounders. Additional studies, including prospective cohort studies and large well-controlled registry studies examining the impact of insurance on survival and financial burden, could confirm current findings and delve into key subgroups.

Almost no current research is focused on important outcomes beyond survival and financial burden, such as the impact of insurance on clinical trial participation, quality of care, HRQOL outcomes, TRAEs, and cancer recurrence. Access to trials, in particular, has been of longstanding interest to policymakers; Congress recently passed the Clinical Treatment Act to improve trial-related coverage for Medicaid beneficiaries. Implementation of this law would be enhanced by research exploring whether uninsurance or underinsurance might continue to act as a barrier to trial participation in the future, as well as the reforms that would be needed to address such barriers in full.

Few studies have focused on diverse racial and ethnic groups, patients with low income, Medicaid beneficiaries, uninsured patients, and patients residing in rural settings. Similarly, relatively few studies have focused on adolescents and young adults, and just 14 studies (9%) focused on families with a pediatric patient. As a result, little is known about the impact of insurance on blood cancer care within these vulnerable populations. Although policymakers have expressed commitments to addressing health disparities, evidence-based policymaking in this area will be constrained by the gaps in this literature.

No peer-reviewed studies have examined blood cancer outcomes related to short-term, limited-duration health plans and other types of insurance-like products (eg, fixed indemnity plans or health care sharing ministries) that do not comply with the ACA’s market reforms and thus require plan enrollees to assume significant financial risk. With several million people already enrolled in some of these plans types, it is critical to know the extent to which such coverage contributes to large-scale financial toxicity for patients living with costly diseases like blood cancer.

No studies have evaluated the implementation of interventions designed to improve access to or use of insurance among patients with blood cancer (eg, patient navigators focused on insurance access; insurance-related education programs). Implementation research should examine the methods and strategies that facilitate the uptake of evidence-based insurance-related programs and guidelines into practice. Such research would be timely because the Biden administration has identified increased enrollment in qualified health plans as necessary to stabilize the ACA’s insurance marketplaces, and policymakers have recently expressed a desire to curb broker practices that steer unwitting patients to inferior health insurance plans.54

**Conclusions** The current body of peer-reviewed literature provides evidence that insurance status and type affect OS and financial burden for patients with blood cancer. However, evidence is insufficient on the impact of insurance on other important outcomes, including clinical trial participation, quality of care, and HRQOL. In addition, evidence specific to key vulnerable populations is insufficient. Further research is needed to guide policymaking in these areas and to help patients effectively navigate the health insurance marketplace, gain better access to high-quality care, and achieve better health outcomes.

**AUTHOR INFORMATION.** Karen Crotty, Katherine Treiman, Candis Winas, and Catherine Yavor are with RTI International; Maralanea Lee, Maria Gao-Meu, and Elisa Winas are with The Leukemia & Lymphoma Society.

**CORRESPONDING AUTHOR.** Karen Crotty, RTI International, 5040 E Cornwallis Road, Hobbs 139, P.O. Box 12194, Durham, NC 27709. E-mail: kcroty@rti.org.

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Clinicians and Payers Expect to Wait and See Before Embracing CMS’ MIPS Value Pathways

ERIN CRUM, MPH

CONTINUED FROM SP245

Although the program’s intentions are good, stakeholders have shared criticism of potential structural flaws in MIPS; these flaws may serve to prevent widespread adoption and discourage commercial payers from fully embracing the program and similar risk arrangements structured around value-based care. CMS is attempting to rectify many of these critiques about MIPS by introducing MIPS Value Pathways (MVPs).1 MVPs are disease state- or specialty-specific subsets of measures and activities that consolidate core concepts across the 4 separate performance areas in MIPS.

A closer look at what CMS is attempting to do with these specialty-specific MVPs, as well as ways they can be made more successful than MIPS, may provide some useful insight for clinicians and payers.

MVPs Strive to Eliminate Cherry-Picking of Quality Measures and Improvement Activities

One concern with the MIPS program is that it provides clinicians with full autonomy to select the quality measures and improvement activities that they want to report. The 4 performance areas—quality, improvement activities, promoting interoperability, and cost—are very siloed, rather than integrated. In its current format, clinicians can select quality measures where their performance is high, even if the measures are not relevant to the core activities of their area of specialty. Furthermore, clinicians can select from a full list of improvement activities for their 90-day attestation, even if the activity has been fully adopted at the practice for several years. In such cases, CMS is not achieving the intent of the program by stretching clinicians to adopt new, innovative solutions to drive improved patient care.

The new MVPs attempt to eliminate these silos and target the issue of cherry-picking, along with some other fundamental flaws in the MIPS program. To achieve this, CMS has indicated that the new MVPs promote targeted concepts across the 4 MIPS categories, making the program more meaningful and valuable by having clinicians report on measures and activities specific to their areas of practice. Different specialties will have a core set of measures relating to their areas of care that clinicians will be obligated to choose from, rather than selecting their top-performing measures from the full menu of quality measures and improvement activities. CMS’ vision is to create a core set of measures and activities that are complementary and drive improvements in patient care, targeting specific disease areas or specialty care.

Factors That May Inhibit MVPs’ Success

While creating a framework for more specialty-specific and meaningful participation in the MIPS program through MVPs is positive movement in the right direction, many issues will apparently still need to be addressed before widespread adoption is likely to occur and for the program to become successful and viable for the long term. These include the following:

NEED FOR CLARITY ON SCORING METHODOLOGY FOR MVP VS. TRADITIONAL MIPS PARTICIPANTS. CMS recently published the 2022 Proposed Rule containing additional criteria for MVPs. Contained in the Proposed Rule, CMS further described the potential scoring methodology. CMS has proposed to reduce the reporting burden for MVP participants by requiring 4 quality measures from a MVP-specific measure set instead of the 6 required by traditional MIPS that can be selected across an inventory of approximately 200 measures. This will certainly help reduce “cherry picking” of measures where clinicians select measures based on performance, rather than relevance to the area of medicine for that specialty clinician. However, there is no timeline for when the transition to MVPs will be required and not optional. It seems that there should be scoring considerations to incentivize specialty clinicians to adopt MVPs to even the playing field with those who choose to continue participating in traditional MIPS.

Additionally, for some specialties, no measures are applicable in certain categories. For example, no-specific episode-based cost measures are appropriate for medical oncology. There is a single, broad total per capita cost measure, which is more relevant to primary care services provided to Medicare patients. If CMS determines that this cost measure is not appropriate, how would CMS reweight the points for the cost category to make sure it is still fair across the board? Simply put, many questions around how scoring will occur are still open.

OPTIONAL PARTICIPATION WILL PERPETUATE ADOPTION LAG. CMS is currently planning a gentle, phased-in rollout for MVPs, which ultimately may make it optional for many clinicians. This may slow adoption of the program and create difficulties for the incentives and penalties associated with the MVP. With low participation, the necessary funds will be lacking to pay incentives, since funding for the incentives is supposed to come from penalties paid by poor performers. But with low participation, very few practices will be penalized, providing very limited funds for incentives. This is the same situation as exists in MIPS, where the incentive payment has been hovering around 1%. Performers in the top 80% to 90% are earning an adjustment of only 0.9% to 1.2%. These practices have invested significant dollars to implement MIPS, so many feel it has not been worth the investment.

DELAYED INFORMATION FROM CMS DOES NOT PROVIDE ACTIONABLE DATA FOR PARTICIPANTS. One of the biggest issues practices have articulated regarding MIPS—which will likely also be an issue with MVPs—is that the program is retrospective and provides no actionable data. Practices are just now seeing their MIPS positive or negative adjustments from their participation in 2019, representing a 2-year delay. Additionally, CMS does not provide actionable feedback throughout the year that would enable clinicians or practices to better understand areas for improvement. Consequently, no ongoing feedback or identification of patients is included in the practice’s MIPS scoring (specifically, their cost measure and patients who will be attributed to them), so they are unable to effectively manage their patients’ overall cost of care nor to implement processes during the performance year that would lead to effective improvements in quality care and cost efficiencies.

Without some kind of timely data sharing that provides meaningful information—meaningful enough for practices to adjust the care they provide—MIPS Value Pathways will most likely struggle the same way MIPS has.
Making MVPs More Successful Than MIPS
Since the new MVPs are still in the developmental stage, CMS has opportunities to address issues that could help ensure long-term success. First and foremost, CMS must provide better access to data for clinicians, technology vendors, and measure developers.

Clinicians need timely data to make positive, effective change throughout the performance year, so information is meaningful, actionable, and current. Technology vendors need CMS to supply data and funding, as they are currently burdened to develop solutions and incorporate data sets to provide feedback to clinicians. However, there is no money in MIPS submissions due to low participation. Measure developers face similar problems, with no resources to develop data that would enable them to better develop measures that leverage information from multiple sources. A positive approach would be for CMS to make available claims data and other data sources that developers could then incorporate into more meaningful quality measures.

Over the years, CMS has outsourced certain responsibilities for measure and registry development and support to third parties, including registries, state societies, specialty societies, and organizations like McKesson. However, these endeavors are costly, and there is no incentive to develop or support these measures when there is no revenue in the program for these activities. By incentivizing—ie, funding certain measure development or providing resources to support the measures once they are established—CMS could ensure that experts stay involved and perhaps even encourage more collaboration across key stakeholders to develop meaningful measures.

The new MVPs should also align with other programs, such as the Oncology Care Model (OCM),1 the Radiation Oncology (RO) Model, and Primary Care First.2 By ensuring that the MVPs are developed such that they align with other regulatory programs and initiatives, the same core messages can be used across the practice to support quality care. For example, the measures in the OCM could align with the measures CMS selects for the oncology MVP core set of measures. Having this alignment would likely drive incorporation of these core measures and activities as part of managed care payer arrangements.

By aligning under some core values or initiatives from these programs, practices can take certain activities across the entire patient population and monitor their success for all patients. This encourages measuring things that matter, enabling clinicians to “buy in” on a core set of services or activities that are applicable for all of their patients, regardless of a patient’s participation in a particular program. This alignment facilitates development of processes and procedures across the care team that focus on the core areas. These activities—including advance care planning, depression screening, and pain management, to name just a few—are essential components of care. Under the practice will provide for every patient, as they are part of the right clinical approach and are also critical components of high-quality, comprehensive cancer care.

Not only should the new MVPs align across programs, they should also align components within the quality measure sets that drive improved patient-centered care and emphasize initiatives known to be associated with reduced health care costs and improved outcomes in oncology. To be successful, the MVPs should be outcomes-focused, and not just broad-based process measures.

**McKesson and The US Oncology Network Collaborate on a Patient-Centric MVP**
McKesson, a leader in advancing value-based care, has collaborated with The US Oncology Network (The Network), a network of independent, physician-owned community practices, to develop an oncology-specific MVP; it has been submitted to CMS for consideration to be included in the future MIPS framework. The Network represents more than 10,000 oncology physicians, nurses, clinicians, and cancer care specialists nationwide, and the organization was instrumental in gathering input for the proposal.

This MVP addresses legitimate ways to improve specialty care and the patient experience, while reducing costs, when possible, through a more integrated approach than the current MIPS framework. It offers opportunities to improve the quality of care and value for cancer patients, as well as measures and activities that foster care coordination across care teams. This ensures patient-centric, personalized care that aligns with patients’ goals and wishes.

Unlike the existing MIPS program, the quality measures and improvement activities in McKesson’s MVP are meaningful to oncology. They measure items that matter to the oncology clinician, rather than holding them accountable for management of health care concerns better managed by other specialists, such as diabetes or other chronic conditions. The quality measures focus on components of care that prioritize patient involvement and the patient’s voice, which are critical to optimizing patient-centered oncology care. Many of the improvement activities stress shared decision-making in treatment choices, a core tenet of value-based care. Patient involvement is emphasized in such activities as development of a care plan and advance care planning initiatives; this fosters meaningful discussions with patients about their values and goals for treatment and end-of-life care.

With a strong emphasis on incorporating the patient voice to drive improvements in oncology care, McKesson’s MVP includes 2 patient-reported outcome measures: one to measure improvement in pain management, and a second that utilizes a comprehensive, oncology-specific patient survey to assess various aspects of cancer care and the patient experience. Gauging patients’ attitudes about their care and experiences paves the way to employ an exciting new area of research called mindsets—core assumptions about the nature and workings of things that can influence the mental and physical health of patients with cancer, potentially improving their outcomes.3 The MVP provides a strong framework for implementing targeted psychological interventions from the care team that aim to instill more positive mindsets in patients to drive better outcomes.

Through similar measure selection, care plan development, and integration of the patient experience survey—all components of care that help improve quality and cost—McKesson’s MVP aligns with existing and proposed programs in the Center for Medicare and Medicaid Innovation (CMMI), such as the OCM, Oncology Care First, and the RO Model. By providing a similar framework and areas of focus as existing CMMI programs, the MVP serves as a vehicle to incrementally phase clinicians into alternative payment models and to create a sense of alignment to reinforce key activities on oncology care. Focusing on the core areas of care enables the care team to provide an enhanced suite of services under the value-based care umbrella, treating all patients equally without thinking about whether a patient is participating in a particular program.

Managed care will find many positives in McKesson’s patient-centric MVP, as it is designed to drive and support the delicate balance of improved quality with lower costs that value-based care requires, all while ensuring that the patient’s voice is strongly heard.

**Wait-and-See Approach**
Commercial payers will be keeping a close eye on what happens with the new oncology-specific MVPs. Because many questions still exist around whether quality measures actually have a meaningful impact on patient outcomes and reducing costs, payers have been slower to truly integrate quality measures into value-based care arrangements. All stakeholders, including payers, are anxiously waiting to see how these programs perform and whether they meet hoped-for expectations. Payers tend to follow the government’s lead, but until many of the details are clearly defined within the regulatory programs and they are running smoothly, payers will most likely take a wait-and-see approach. They will also be looking for clear-cut evidence that these programs are effective in supporting value-based care before confidently moving forward.

**AUTHOR INFORMATION**
Eric Crumm, MPH, is the director of quality measurement strategy for McKesson.

**REFERENCES**
Bo Gamble, COA’s director of strategic practice initiatives, told The American Journal of Managed Care® that the new standards were developed with a multistakeholder team of physicians, a nurse, patient advocates, and leaders from employer coalitions who fund health care. The updated standards reflect the addition of the domains to elevate the importance of end-of-life care and adherence to QOPI certification, he said.

The hope is that payers can coalesce around a common set of pay-for-performance standards, as well with regard to care delivery. All oncology payment models have 3 basic elements, Gamble said: care delivery, payment methodology, and performance measures. He pointed to research that was presented by COA indicating that its members deal with up to 35 different oncology payment models across public and commercial plans. 2

“This is getting crazy,” Gamble said. Such diversity becomes impossible for practices to manage. It would be preferable, he said, to reach agreement with payers to at least standardize the platform for care delivery, with payers differing on the payment methodology.

Some experts have said that a multimodel system can be unethical, if physicians feel the evidence points to one method being superior.

Will payers buy in? Gamble is encouraged by early discussions as COA works with ASCO on the upcoming OMH certification pilot. “So far, so good,” he said. Compared with the last iteration of the OMH, “this program is much more structured and goal-oriented.”

This pilot, he said, will address a major weakness of the current OMH: A dashboard will gather clinical data to offer real-time information that includes comparisons with peers. The information delay in the current Center for Medicare and Medicaid Innovation (CMMI) program means providers find out about weaknesses well after the fact.

With oncology practices still waiting to hear what will come after the OCM ends in 2022, 6 “We hope that CMMI will take notice,” he said.

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