COMMENTS

Empower Physicians to Fight Financial Toxicity With Biosimilars
Kathy Oubre, MS

ONGOING PRACTICES SEE THE TOLL. Financial toxicity1 exacts on patients and their families every day. The financial burdens of cancer treatment are damaging even when they don’t directly affect care—and research shows that all too often, they do. Patients struggling under the burdens of cancer care are more likely to be nonadherent with their prescribed treatment regimen, failing to fill prescriptions, delaying office visits, and forgoing critical diagnostic tests.2 More affordable care is better care, and payers should empower providers to steer patients toward superior-value options whenever available. When it comes to oncology biologics, this means giving providers the power to prescribe biosimilars.

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ADVOCACY PERSPECTIVE

Improving Survival in Lung Cancer: Commitment of The Lung Ambition Alliance
Giorgio Scagliotti, MD, PhD

FOR TOO LONG, lung cancer has had one of the worst prognoses of any cancer. It is the leading cause of cancer-related deaths worldwide (Figure 1); only 1 in 5 people with lung cancer will be alive 5 years after diagnosis.1,2

New advances are creating the opportunity to transform the diagnosis, treatment, and management of lung cancer. However, survival rates have improved only modestly and are lagging behind those of other common cancers (Figure 2).3 The time for us to act is now: to come together as a community, to bend the lung cancer survival curve faster, and to significantly improve patient outcomes in this devastating disease.

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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, hematuria 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.

BRUKINSA IS NOW APPROVED
BRUKINSA™ (zanubrutinib) 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.

Learn more at BRUKINSA.com

Embryo-Fetal Toxicity
Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryofetal 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.

ADVERSE REACTIONS
The most common adverse reactions in > 10% of patients who received BRUKINSA were decreased neutrophil count (33%), 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 (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

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.

Please see Brief Summary of full Prescribing Information on the following pages.
Both trials excluded patients with prior allogeneic hematopoietic stem cell transplant, exposure to a BTK \( \geq 50 \times 10^9 /L \) and an absolute neutrophil count \( \geq 1 \times 10^9 /L \) independent of growth factor support, hepatic enzymes \( \leq 2.5 \) times upper limit of normal, and prior radiation to the central nervous system.

5.2 Infections

Infections and infestations occurred in 13% of patients treated with BRUKINSA monotherapy. Grade 3 or higher infections were pneumonia (11%) and hemorrhage (5%). Fatal cases included pneumonia in 2 patients and cerebral hemorrhage in one patient.

6 ADVERSE REACTIONS

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

- Hematologic
- Infections
- Pneumonia
- Secondary Primary Malignancies
- Cardiac Arrhythmias
- Embryo-Fetal Toxicity

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-3111-206, BGB-3111-205, BGB-3111-210, and BGB-3111-1002 and to BRUKINSA at 300 mg once daily in 105 patients in trials BGB-3111-AU-003 and BGB-3111-1002. Among 629 patients receiving BRUKINSA, 76% 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 in > 10% of patients who received BRUKINSA were neutrophil count decreased (53%), platelet count decreased (59%), upper respiratory tract infection (38%), and diarrhea (30%).

6.2 Laboratory Findings

The following non-hematologic findings occurred in \( \geq 20\% \) of patients treated with BRUKINSA monotherapy in clinical trials:

- Chemistry abnormalities
- Blood urea nitrogen increased
- Creatinine increased
- Calcium increased
- Phosphorus decreased
- Magnesium decreased
- Lactic dehydrogenase increased
- Alanine aminotransferase increased
- Aspartate aminotransferase increased

7.1 Effect of Other Drugs on BRUKINSA

Prevention or management

- Co-administration with a moderate or strong CYP3A inducer
- Co-administration with a moderate or strong CYP3A inhibitor

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Males

Advise males to use condoms during treatment and for at least 1 week after the last dose. If this drug is used in a pregnant woman, it should be apportioned of the potential hazard to a fetus [see Use in Specific Populations (8.1)].

Females

Advise women to avoid becoming pregnant during treatment and for at least 1 week after the last dose. If this drug is used in a pregnant woman, it should be apportioned of the potential hazard to a fetus [see Use in Specific Populations (8.1)].

8.2 Lactation

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 in the nursing child, advise breastfeeding mothers not to breastfeed while receiving this drug [see Use in Specific Populations (8.2)].

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Use in patients age \( \geq 65 \) years has not been fully evaluated. Use in patients age \( \geq 65 \) years should be limited to patients for whom the potential benefits outweigh the potential increased risks of serious adverse reactions.

8.6 Renal Impairment

Dose modification of BRUKINSA is recommended in patients with severe renal impairment (CLcr < 30 mL/min) or on dialysis.

8.7 Hepatic Impairment

Dose modification of BRUKINSA is recommended in patients with severe hepatic impairment (Child-Pugh class C) or moderate hepatic impairment (Child-Pugh class B).

8.8 Tobacco Use

BRUKINSA is not indicated for patients with current or recent tobacco use and should be avoided in patients with active or recent history of tobacco use.

8.9 Concomitant Use of Drugs

Coadministration with a moderate or strong CYP3A inhibitor may increase the risk of BRUKINSA toxicities. Coadministration with a moderate or strong CYP3A inducer may reduce BRUKINSA efficacy.

8.10 Special Populations

8.10.1 Pregnancy

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant animal. Pregnant rats were exposed to the recommended dose of 160 mg twice daily for 6 months during organogenesis. Administration of zanubrutinib to pregnant rabbits during the period of organogenesis was associated with embryo-fetal toxicities, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily for 6 months. Advise pregnant women to avoid becoming pregnant during treatment and for at least 1 week after the last dose. If this drug is used in a pregnant woman, it should be apportioned of the potential hazard to a fetus [see Use in Specific Populations (8.1)].

8.10.2 Breastfeeding

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. Advise breastfeeding mothers not to breastfeed while receiving this drug [see Use in Specific Populations (8.2)].

8.10.3 Other concomitant medications

BRUKINSA is not indicated for patients with current or recent tobacco use and should be avoided in patients with active or recent history of tobacco use.

8.10.4 Effect of other drugs on BRUKINSA

Based on in vitro CYP3A inhibition and human interaction studies, co-administration with a moderate or strong CYP3A inhibitor is expected to increase zanubrutinib plasma concentrations, which may increase the risk of BRUKINSA toxicities. Co-administration with a moderate or strong CYP3A inducer is expected to decrease zanubrutinib plasma concentrations, which may reduce BRUKINSA efficacy.

8.11 Other Special Populations

Other clinically significant adverse reactions that occurred in ≤ 10% of patients with mantle cell lymphoma include major hemorrhage (defined as ≥ Grade 3 hemorrhage or CNS hemorrhage of any grade), hypertension (5%), and headache (5%).

Table 4: Selected Laboratory Abnormalities* (> 20%) in Patients with MCL who received at least one prior therapy in clinical trials BGB-3111-AU-003 and BGB-3111-AU-002

- Neutrophils decreased
- Platelets decreased
- Hemoglobin decreased
- Hemoglobinopathy
- Lymphocytes
- Blood urea nitrogen increased
- Creatinine increased
- Calcium increased
- Phosphorus decreased
- Magnesium decreased
- Lactic dehydrogenase increased
- Alanine aminotransferase increased
- Aspartate aminotransferase increased
- Iron decreased
- Ferritin decreased
- Transferrin decreased
- Albumin decreased
- Total cholesterol increased
- High-density lipoprotein cholesterol increased
- Low-density lipoprotein cholesterol increased
- Hemoglobinopathy

Table 4: Laboratory Parameter

- Neutrophils decreased
- Platelets decreased
- Hemoglobin decreased
- Lymphocytes
- Blood urea nitrogen increased
- Creatinine increased
- Calcium increased
- Phosphorus decreased
- Magnesium decreased
- Lactic dehydrogenase increased
- Alanine aminotransferase increased
- Aspartate aminotransferase increased
- Iron decreased
- Ferritin decreased
- Transferrin decreased
- Albumin decreased
- Total cholesterol increased
- High-density lipoprotein cholesterol increased
- Low-density lipoprotein cholesterol increased
- Hemoglobinopathy

* Based on laboratory measurements.
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 CYP3A Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Impact:</td>
</tr>
<tr>
<td>• Co-administration with a moderate or strong CYP3A inhibitor increases zanubrutinib C₀ and AUC (see Clinical Pharmacology [12.3]) which may increase the risk of BRUKINSA toxicities.</td>
</tr>
<tr>
<td>Prevention or management:</td>
</tr>
<tr>
<td>• Reduce BRUKINSA dosage when co-administered with moderate or strong CYP3A inhibitors [see Dosage and Administration (2.3)].</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate and Strong CYP3A Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Impact:</td>
</tr>
<tr>
<td>• Co-administration with a moderate or strong CYP3A inducer decreases zanubrutinib C₀ and AUC (see Clinical Pharmacology [12.3]) which may reduce BRUKINSA efficacy.</td>
</tr>
<tr>
<td>Prevention or management:</td>
</tr>
<tr>
<td>• Avoid co-administration of BRUKINSA with moderate or strong CYP3A 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 for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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 heart) 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 16 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 52 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 postweaning, 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, nor 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 Populations (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

Safety and effectiveness in pediatric patients have not been established.

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)].
IN 2018, THE FDA approved 19 drugs, 4 biosimilars, and added 38 indications for therapies that fight cancer.1 The pace continued in 2019: of the 41 new agents approved through November, 13 are used in cancer or blood disorders.2 This period of innovation is likely to continue, and even accelerate, due to the FDAs willingness to examine real world data and alternative approval endpoints,3 offering evidence that research focused on rare cancers, or improving outcomes and reducing toxicities, is having an impact.4 However, innovation has come at a price. In 2018 spending on cancer medicines rose by 12.9%,5 while the overall US inflation rate was only 1.9%.6 Controlling healthcare costs dominates nearly all other considerations in the political debate over healthcare reform. For federal policymakers, ensuring the sustainability of the Medicare Trust Fund is central to all considerations for future CMS care and reimbursement models.7 These concerns have delayed CMS development of reimbursement models for emerging cancer treatment technologies, such as chimeric antigen receptor (CAR) T-cells. Fears about the Medicare Trust Fund and healthcare-related inflation have propelled CMS leadership to increase the level of risk that clinicians and healthcare systems bear in care delivery. The inclusion of advanced alternative payment models (APMs) within the Medicare Access and CHIP Reauthorization Act of 2015 show the importance of bringing greater cost accountability and transparency to physicians and healthcare systems.8 Unfortunately, this adds administrative burdens and ironically holds physicians accountable not only for the costs that they can control, but also for those they cannot control, such as the proper use of high-cost pharmaceuticals.9 Thus, physicians and healthcare systems are disempowered from leading meaningful, sustainable innovation efforts and have at best highly imperfect models through which they can follow the lead of the agency. In this issue of Evidence-Based Oncology™ we examine this issue from multiple perspectives. Kathy Uhre, MS, provides perspective on biosimilars that may provide an innovative paradigm for blunting the cancer pharmacologic rate of inflation. Keely Macmillan, MPH, provides an overview of the proposed Oncology Care First (OCF) model and how it may or may not lead to better incentives for physicians to practice value-based cancer care. Finally, Associate Editor Kashyap Patel, MD, provides one of 2 physician perspectives on the OCF model. We must not forget that physicians and healthcare systems that actually care to provide care to patients are essential incubators for transformational ideas that bring us closer to realizing the full potential of the value-based cancer care paradigm. For physicians and cancer care systems to lead this transformation, they need to be allowed to lead and innovate in an unfettered way. Alternative APMs must give physicians flexibility to succeed in the pursuit of economically sustainable cancer care. Physicians should never be penalized for delivering the most appropriate care to their patients, even if it is more expensive. The future of increasing effective cancer care that better serves patients and their families is dependent upon ensuring that physician and healthcare system leaders are allowed to move forward, at speed and empowered to succeed in making this future a reality. Joseph Alvareñas, MD

REFERENCES
The rise of the nurse navigator in oncology care has been recognized as one of the positive changes under the Oncology Care Model (OCM). CMS has proposed a successor model, Oncology Care First, to replace the OCM in 2021.

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KELLY DAVIO

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ADVOCACY PERSPECTIVE

Improving Survival in Lung Cancer: Commitment of The Lung Ambition Alliance

GIORGIO SCAGLIOTTI, MD, PHD

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Passion for Innovation.
Compassion for Patients.™
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On to the Next Wave of Payment Reform

TO UNDERSTAND HOW FAR we have come in cancer care delivery, read what Terrill Jordan, president and chief executive officer of Regional Cancer Care Associates (RCCA), told fellow stakeholders at the Community Oncology Alliance Payer Exchange Summit in late October: “In 2012, if I had said, ‘We are going to 2-sided risk,’ I would not have a job. Today I say, ‘We’re going to 2-sided risk,’ and they ask, ‘How?’”

After years of denying, complaining, and resisting, oncologists who want to stay in practice are waking up to reality: Value-based care is here to stay. Leading edge practices like RCCA paved the way for the rest with the Oncology Care Model (OCM), which was CMS’ first effort with a multi-payer alternative payment model.

To be sure, the OCM has its flaws. Some practices delivered high-quality care but saw too many patients with the wrong type of cancer, or they gave patients cutting-edge therapies never envisioned in OCM formulas. Doctors here say innovation has outpaced the mathematical model and their practices pay the price. In a paper that appeared in JAMA Oncology October 31, 2019,1 authors from Tennessee Oncology and Tuple Health demonstrated that this is true. There is little question the OCM needs a fix.

But in many ways the OCM has transformed cancer care for the better. No oncologist who has observed the difference that nurse navigators make in patients’ lives, overlaid the clinic schedule to see patients on a same-day basis, or witnessed what a nutritionist can do for patients wants to return to “before” the OCM. The challenge now is to keep what works and fix what doesn’t. As the doctors said to Jordan, the question is “How?”

CMS has released the outline of Oncology Care First (OCF), which would be the successor to OCM if approved before January 2021. As we discuss throughout this special policy update of Evidence-Based Oncology™, the new model drills down to the differences between the cost of treating various cancers. It also calls for electronic collection of patient-reported outcomes, a shift that some who spoke with us like in theory but warn will require care to work through in practice.

Most of all, OCF continues the push toward asking physicians to act like entrepreneurs—to be willing to take risks with the promise of reward for delivering better care at a lower cost. If that’s the case, CMS and other payers would be wise to loosen the reins on practices and let them take ownership of choices.

As Kathy Oubre, MS, writes in a commentary about the need to expand use of biosimilars, practices can’t be expected to keep separate therapies on hand for every payer.

These are times of great innovation, but that requires communication both ways, where the ideas can flow from those on the front lines up, not from the top down.

Sincerely,
Mike Hennessy, Sr
Chairman and Founder

REFERENCE
NOW APPROVED

Learn more about ROZLYTREK (entrectinib) at www.ROZLYTREK.com/hcp.
Hope and Some Skepticism: Whether Oncology Payment Models Will Work

Allison Inserro

JUST OVER A WEEK before CMS revealed some of its thinking on the future of oncology value-based care, oncologists and others who crowded into a Nashville, Tennessee, ballroom at the end of October shared their thoughts, successes, and frustrations regarding the current Oncology Care Model (OCM).

At certain points during the latest installment of the Institute for Value-Based Medicine®, an initiative of The American Journal of Managed Care®, it was hard to tell if the physicians and healthcare executives were thinking about January 2020 or January 2021.

Next month, oncology practices participating in the OCM must decide whether to accept 2-sided risk. Come January 2021, CMS plans to start Oncology Care First (OCF), the successor to OCM; on November 1, it released a request for information (see Cover).

“IT Sounds scary, but I hope you leave tonight inspired, because I think we’re ahead of the game on this,” said Stephen M. Schleicher, MD, MBA, cochair of the meeting, an oncologist at Tennessee Oncology, and chair of the Quality and Value Committee of OneOncology, a network of community oncology practices. According to Schleicher, the oncology community should focus on 3 steps:

• Understanding the models in-depth because value-based care (VBC) is here to stay.
• Educating payers on how to improve their models to make sure that cost control does not come at the expense of patients.
• Optimizing care coordination to prevent avoidable emergency department (ED) visits and hospitalizations, facilitate end-of-life care planning, and avoid unnecessary tests and pharmaceutical use.

“The think before that PET [positron emission tomography] scan if you need it, think before that expensive drug, if we have a biosimilar instead,” he said, offering up examples.

Darin Gordon, who is widely credited with turning around TennCare, the state’s $10.5 billion Medicaid managed care program, described how it took him a few years to “learn into” the idea of VBC and value-based purchasing (VBP).

As part of his presentation, he reviewed a VBP framework, created by the Health Care Payment Learning & Action Network, which created a pathway for describing alternative payment models. The 4 classifications include category 1, fee for service (FFS); 2, FFS and a link to quality and value; 3, alternative payment models built on an FFS architecture; and 4, population-based payment.

Gordon said that even after he “fully embraced” VBP, he had to again change his thinking. “I’ll just say this: As a self-diagnosed value-based purchasing zealot…where I literally thought we should buy light bulbs on a value-based purchasing agreement, after going through it, you discover there is a lot of stuff that value-based purchasing isn’t suited for.”

At the same time, he said, “there’s a big belief in the industry that we don’t arrive [to VBP] until we get everyone to category 4.1 don’t think that’s right, either.”

Although the categories may seem like a continuum, with some organizations falling into category 2 or 3 because it works best for them, the only thing you won’t find, he said, is anyone defending FFS. There is plenty of evidence that FFS does not work, even if the evidence on VBP is not yet conclusive.

Instead, fueled by rising healthcare costs, there is an overwhelming sense from payers that “we have to try something different,” he said. Oncology is spread among all 4 categories—commercial, Medicare, Medicaid, and the exchanges.

In Tennessee, Gordon said he saw wide variability in cost from provider to provider, a difference of as much as 3 to 6 times that couldn’t be explained.

“We needed more tools to incentivize quality improvement,” he said. However, he said, he didn’t want to tell doctors what to do or how to do it: “I want to…create a dynamic [in which] the provider could start asking different questions, should be asking different questions.”

At the time, Vanderbilt University had a tool to connect patients to doctors via text. Although they didn’t get reimbursed for it, the institution was large enough to absorb the cost, according to Gordon. At that point, he said, he realized he could use the state’s Medicaid program to change reimbursement for physicians who had already told him, “We know what we need to do for patients, and we also know we won’t get paid for doing those things.”

“That was a big driving force for this,” he said.

“As a care delivery model, the [Oncology Care Model] is awesome, but Medicare did not go into this to improve the quality of cancer care. They went into this to save money.”

Michael Kolodziej, MD, FACP, ADVI Health

Gordon addressed some advocacy groups’ concern that VBP agreements can be used to restrict access to certain treatments: “Actually, it’s just creating different questions that the providers themselves—that clinician—[will] ask themselves in ensuring that they have the best possible outcome for that member.”

When VBP functions at its highest level—when payers, providers, and patients work together to improve health—he said, “quite frankly, a lot of discussions about prior authorizations are meaningless.” He added, “I don’t care as much, because you’re fully at risk.”

Although Gordon said he believes that VBP will remain firmly on landscape, Michael Kolodziej, MD, FACP, vice president and chief innovation officer at ADVI Health, was decidedly less upbeat.

“I’m going to disagree with just about everything you just said,” he told Gordon, then said commercial payers look at oncology practices the same way Willie Sutton looked at banks: “That is where the money is.”

“’How did we get into this mess?’ Kolodziej asked. “The cost of taking care of cancer patients in the [United States] has exploded largely as a consequence of the cost of drugs that have brought great value for our patients but at a significant price, and the rate of the trend so far exceeds the average person’s income that
nearly everybody says [it is] unsustainable,” he said, launching into a review of the first alternative payment models in oncology.

When Kolodziej was in charge of oncology strategies at Aetna, he participated in the OCM when it launched. “As a care delivery model, the OCM is awesome, but Medicare did not go into this to improve the quality of cancer care. They went into this to save money,” he said. “The payment is based on this goofy methodology that they developed, and I think anybody who spent time thinking about this recognizes that the model is way too complicated, just way too complicated.”

So, after 4 performance periods, what have oncologists learned? There are problems with various parts of the model, Kolodziej said, which has been adjusted several times. Yet, even as savings increased, in his view, 90% of the participating oncology practices have no idea why they generated savings. “This model does not fix their pain,” he said, because it does not address the cost of drugs.

When he was at Aetna in a partnership with Texas Oncology, using the ClearPath pathway saved 20% of the cost of care. He attributed that to the use of pathways, not Aetna’s medical home. He also challenged the notion that payers consist only of health insurance plans. The employers are the payers, he said, and they are complaining loudly to health plans.

“We have a long history [over the past] 20 years of paying too much for stuff that doesn’t work. We got some stuff now that works. That makes it really challenging,” he said, citing study findings that showed no link between the marginal added benefit of new drugs and the launch price.1

Referring back to the next iteration of the next oncology care model to come out of the Center for Medicare and Medicaid Innovation, Kolodziej was pessimistic: “I think that they cannot have a care model in which 85% of oncologists in the [United States] cannot participate, and that’s what CMS is right now.” Alternative payment models are not cutting it, he said.

Hearkening back to the idea of using new tools to drive improvement, Robert Daly, MD, MBA, of Memorial Sloan Kettering Cancer Center (MSKCC), explained how the center uses predictive data analytics to improve care for patients by meeting CMS quality measures for avoiding preventable hospitalization due to 9 conditions: neutropenia, fever, pain, dehydration, anemia, pneumonia, sepsis, nausea, and diarrhea.

With proactive care and increased communication, these can be managed in outpatients, he said. Why is this an issue? Patients on active treatment have 1 hospital admission and 2 ED visits per year; about 50% of those ED visits and 40% of the admissions are related to treatment toxicities, for 3 main reasons, Daly said:

- Patients are not being equipped to manage adverse effects at home.
- Patients assume little can be done to help them and don’t seek care until symptoms worsen.
- Communication varies between the patient and the clinician.

“As anyone who has treated cancer patients knows, they’re not just coming in with 1 symptom—they’re coming in with clusters of symptoms,” Daly said.

Daly said the MSKCC pilot study was inspired by the work of Ethan Basch, MD, MSc, on the effect of patient-reported outcomes (PROs) on survival and quality of life. The 2017 study found that proactive self-management resulted in better outcomes for patients compared with standard of care, including a 30% improvement in quality of life, 7% fewer ED visits, and 5 months’ longer survival.2

The pilot project, called InSight Care, combines PROs with data and proactive care and case management to prevent hospitalizations and ED visits, keeping the patient “in sight” of the provider 24/7 through the use of digital technologies.

Data analytics identifies the highest-risk patients—the 25% of new antineoplastic patients most at risk of arriving at MSKCC’s urgent care center. The risk model helps providers stratify patients to identify who is at high risk of a potentially preventable visit within the first 6 months.

The model combines data from the electronic health record, including laboratory tests, home medications, comorbidities, and psychosocial data, to create a risk score. Doctors can add patients to the high-risk group using an override feature.

In addition, Daly said, the interface that the patient sees is designed to lower barriers to patients’ completion of assessments. The questions have binary answers (yes or no), and the patient can give more details and use an avatar to provide a visual description of symptoms location. The MSKCC staff can tell instantly if the alerts are mild, moderate, or severe. If necessary, the team can see the patient through a specialized video portal, instead of making the person drive into New York City from the suburbs.

As the pilot nears the 1-year mark, Daly said, the results show an effect, with a 59% reduction of high-risk patients visiting the urgent care center. Within the program’s first 30 days, there was a 60% adherence rate of completing assessments; for patients being treated for more than 3 months, a 50% adherence rate.

“That means we’re getting the symptom data from patients every other day on active treatment. That really helps to take better care of them,” Daly said.

Patients love the system, he said, because they know a member of the care team will get back to them within minutes. “They feel that they’re never alone, that there’s this team that is responding to them and helping to get them through their treatment. And they like the remote consultation,” Daly said. Oncologists like the system because they know that their patients are being taken care of while they are busy in the clinic, he added.

Some of the issues that have arisen include trust, Daly said. “This is an extension of the primary team working with the primary oncology teams to manage those symptoms,” he said. “How do we build trust with the primary oncology teams so that they feel those symptoms are being managed in a way that they would want them to be managed?”

In addition, MSKCC initially hired clinicians with experience in palliative, supportive, and symptom care for the project, but as time went, it became clear that patients prefer someone with disease-specific experience.

Of note, when CMS held a listening session November 4 about the OCF model, officials announced that electronic PROs will be required to participate.

REFERENCES
How supplied¹
LIBTAYO is supplied in a carton containing 1 single-dose vial of 350 mg/7 mL (50 mg/mL).

Recommended dosage¹
The recommended dosage of LIBTAYO is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity. Please see brief summary of prescribing information on the following pages for additional dosing and administration information.

The Centers for Medicare & Medicaid Services assigned a 1 mg billing unit for LIBTAYO (1 mg of LIBTAYO = 1 unit). Coding requirements may vary by payer; please verify coding requirements before submitting claims.

Indication
LIBTAYO is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation.

Important Safety Information

Warnings and Precautions

Severe and Fatal Immune-Mediated Adverse Reactions
Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and usually occur during treatment; however, they can also occur after discontinuation. Early identification and management are essential to ensuring safe use of PD-1–blocking antibodies. Monitor for symptoms and signs of immune-mediated adverse reactions. Evaluate clinical chemistries, including liver tests and thyroid function tests, at baseline and periodically during treatment. Institute medical management promptly to include specialty consultation as appropriate.

In general, withhold LIBTAYO for Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions. Permanently discontinue LIBTAYO for Grade 4 and certain Grade 3 immune-mediated adverse reactions. For Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions, administer corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy until improvement to Grade 1 or less followed by a corticosteroid taper over 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids. Institute hormone replacement therapy for endocrinopathies as warranted.

Immune-mediated pneumonitis: Immune-mediated pneumonitis occurred in 2.4% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 3 (0.7%), and Grade 2 (1.3%). Pneumonitis led to permanent discontinuation of LIBTAYO in 1.3% of patients. Systemic corticosteroids were required in all patients with pneumonitis, including 85% who received prednisone ≥40 mg/day or equivalent. Pneumonitis resolved in 62% of patients. 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.

Immune-mediated colitis: Immune-mediated colitis occurred in 0.9% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.6%). Colitis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with colitis, including 60% who received prednisone ≥40 mg/day or equivalent. Colitis resolved in 80% of patients. 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.

Immune-mediated hepatitis: Immune-mediated hepatitis occurred in 2.1% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 4 (0.2%), and Grade 3 (1.7%). Hepatitis led to permanent discontinuation of LIBTAYO in 0.9% of patients. Systemic corticosteroids were required in all patients with hepatitis, including 91% who received prednisone ≥40 mg/day or equivalent. Hepatitis resolved in 64% of patients. Withhold LIBTAYO if AST or ALT increases to more than 3 and up to 10 times the upper limit of normal (ULN) or if total bilirubin increases up to 3 times the ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Please see additional Important Safety Information and accompanying Brief Summary of Prescribing Information on the following pages.

(Continued)
Important Safety Information

Warnings and Precautions (continued)

**Immune-mediated endocrinopathies:** Withhold LIBTAYO if clinically necessary for Grade 2, 3, or 4.

- **Adrenal insufficiency:** Adrenal insufficiency occurred in 0.4% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.2%).
- **Hypophysitis:** Hypophysitis, which can result in hypopituitarism, occurred in 0.2% of 534 patients receiving LIBTAYO, which consisted of 1 patient with Grade 3 hypophysitis.
- **Hypothyroidism:** Hypothyroidism occurred in 6% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.4%); no patients discontinued hormone replacement therapy.
- **Hyperthyroidism:** Hyperthyroidism occurred in 1.5% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.4%); hyperthyroidism resolved in 38% of patients.

- **Type 1 diabetes mellitus:** Type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in 0.7% of 534 patients, including Grade 4 (0.4%) and Grade 3 (0.4%); type 1 diabetes mellitus led to permanent discontinuation of LIBTAYO in 0.2% of patients.

- **Immune-mediated nephritis with renal dysfunction:** Immune-mediated nephritis occurred in 0.6% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.2%). Nephritis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with nephritis, including 67% who received prednisone ≥40 mg/day or equivalent. Nephritis resolved in all patients. Withhold LIBTAYO for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

- **Immune-mediated dermatologic adverse reactions:** Immune-mediated dermatologic reactions, including erythema multiforme and pemphigoid, occurred in 1.7% of 534 patients receiving LIBTAYO, including Grade 3 (1.1%) and Grade 2 (0.6%). In addition, SJS and TEN have been observed with LIBTAYO and with other products in this class. Systemic corticosteroids were required in all patients with dermatologic reactions, including 89% who received prednisone ≥40 mg/day or equivalent. Dermatologic reactions resolved in 33% of patients. Approximately 22% of patients had recurrence of dermatologic reactions after re-initiation of LIBTAYO. Withhold LIBTAYO for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Other immune-mediated adverse reactions: The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 534 patients who received LIBTAYO or were reported with the use of other PD-1– or PD-L1–blocking and PD-L1–blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions. Withhold LIBTAYO for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

- **Neurological:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve paresis, and autoimmune neuropathy.
- **Cardiovascular:** Myocarditis, pericarditis, and vasculitides.
- **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 corticosteroids to reduce the risk of permanent vision loss.
- **Gastrointestinal:** Pancreatitis to include increases in serum amylase and lipase levels, gastritis, and duodenitis.
- **Musculoskeletal and connective tissue:** Myositis, rhabdomyolysis, and associated sequelae, including renal failure, arthritis, and polymyalgia rheumatica.
- **Hematological and immunological:** Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, and solid organ transplant rejection.

Infusion-related reactions

Severe infusion-related reactions (Grade 3) occurred in 0.2% of patients receiving LIBTAYO. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion for Grade 1 or 2, and permanently discontinue for Grade 3 or 4.

**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**

- **Serious adverse reactions occurred in 28% of patients.** Serious adverse reactions that occurred in ≥2% of patients were cellulitis, sepsis, pneumonia, pneumonitis, and urinary tract infection. The most common Grade 3–4 adverse reactions (≥2%) were cellulitis, sepsis, hypertension, pneumonia, musculoskeletal pain, skin infection, urinary tract infection, and fatigue.
- **LIBTAYO was permanently discontinued due to adverse reactions in 5% of patients;** adverse reactions resulting in permanent discontinuation were pneumonitis, autoimmune myocarditis, hepatitis, aseptic meningitis, complex regional pain syndrome, cough, and muscular weakness.
- **The most common adverse reactions (incidence ≥20%) were** fatigue, rash, and diarrhea.

**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 accompanying Brief Summary of Prescribing Information on the following pages.


ALT=alanine aminotransferase; AST=aspartate aminotransferase; PD-1=programmed death receptor-1; NDC=National Drug Code.
LIBTAYO® (cemiplimab-rwlc) injections, for intravenous use

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE
LIBTAYO is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation.

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
The recommended dosage of LIBTAYO is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

2.2 Dosage Modifications for Adverse Reactions
Withhold or discontinue LIBTAYO to manage adverse reactions as described in Table 1. No dose reduction of LIBTAYO is recommended.

Table 1: Recommended Dosage Modifications for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity*</th>
<th>LIBTAYO Dosage Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>Grade 2</td>
<td>Withhold†</td>
</tr>
<tr>
<td></td>
<td>Grades 3 or 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td></td>
<td>Grades 2 or 3</td>
<td>Withhold†</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td></td>
<td>If AST or ALT increases to more than 3 and up to 10 times the upper limit of normal (ULN) or if total bilirubin increases to more than 3 times the ULN</td>
<td>Withhold†</td>
</tr>
<tr>
<td></td>
<td>If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Grade 2, 3, or 4</td>
<td>Withhold if clinically necessary</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Withhold†</td>
</tr>
<tr>
<td></td>
<td>If AST or ALT increases to more than 3 and up to 10 times the ULN</td>
<td>Withhold†</td>
</tr>
<tr>
<td></td>
<td>If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>Grade 3</td>
<td>Withhold†</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td></td>
<td>Recurrent Grade 3 or 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td></td>
<td>Grade 2 or 3 persistent for 12 weeks or longer after last LIBTAYO dose</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td></td>
<td>Requirement for 10 mg per day or greater prednisone or equivalent lasting 12 weeks or longer after last LIBTAYO dose</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Other adverse reactions involving a major organ</td>
<td>Grade 3</td>
<td>Withhold†</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue</td>
</tr>
</tbody>
</table>

Other Adverse Reactions

| Infusion-related reactions | Grade 1 or 2 | Interrupt or slow the rate of infusion |
|                           | Grade 3 or 4 | Permanently discontinue             |

*Severity graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.
†Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Severe and Fatal Immune-Mediated Adverse Reactions
LIBTAYO is a monoclonal antibody that belongs to a class of drugs that binds to the programmed death receptor-1 (PD-1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response with the potential for breaking of peripheral tolerance and induction of immune-mediated adverse reactions. Important immune-mediated adverse reactions listed in Warnings and Precautions may not be inclusive of all possible immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor for symptoms and signs of immune-mediated adverse reactions. Evaluate clinical chemistries, including liver tests and thyroid function tests, at baseline and periodically during treatment. Institute medical management promptly to include specialty consultation as appropriate.

In general, withhold LIBTAYO for Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions.

Permanently discontinue LIBTAYO for Grade 4 and certain Grade 3 immune-mediated adverse reactions [see Warnings and Precautions (5.2)]. For Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions, administer corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy until improvement to Grade 1 or less followed by a corticosteroid taper over one month [see Dosage and Administration (2.2)]. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids. Institute hormone replacement therapy for endocrinopathies as warranted.

Immune-Mediated Pneumonitis
Immune-mediated pneumonitis occurred in 2.4% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%), Grade 4 (0.2%) and Grade 3 (1.1%) [see Adverse Reactions (6.1)]. Pneumonitis led to permanent discontinuation of LIBTAYO in 1.3% of patients. Systemic corticosteroids were required in all patients with pneumonitis, including 85% who received prednisone ≥40 mg per day or equivalent. Pneumonitis resolved in 62% of patients.

Immune-Mediated Colitis
Immune-mediated colitis occurred in 0.9% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.6%) [see Adverse Reactions (6.1)]. Colitis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with colitis, including 60% who received prednisone ≥40 mg per day or equivalent. Colitis resolved in 80% of patients.

Immune-Mediated Hepatitis
Immune-mediated hepatitis occurred in 2.1% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%), Grade 4 (0.2%), and Grade 3 (1.7%) [see Adverse Reactions (6.1)]. Hepatitis led to permanent discontinuation of LIBTAYO in 0.9% of patients. Systemic corticosteroids were required in all patients with hepatitis, including 91% who received prednisone ≥40 mg per day or equivalent. Hepatitis resolved in 64% of patients.

Immune-Mediated Endocrinopathies
Adrenal Insufficiency
Adrenal insufficiency occurred in 0.4% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%), and Grade 2 (0.2%) [see Adverse Reactions (6.1)].

Hypothyroidism
Hypothyroidism, which can result in hypoparathyroidism, occurred in 0.2% of 534 patients receiving LIBTAYO, which consisted of one patient with Grade 3 hypothyroidism.

Hypophysitis
Hypophysitis occurred in 6% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.5%). No patients discontinued hormone replacement therapy for hypophysitis.

Hypophysitis occurred in 1.5% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.5%) [see Adverse Reactions (6.1)]. Type 1 Diabetes Mellitus
Type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in 0.7% of 534 patients, including Grade 3 (0.4%) and Grade 2 (0.4%). Type 1 diabetes mellitus led to permanent discontinuation of LIBTAYO in 0.2% of patients.

Immune-Mediated Nephritis with Renal Dysfunction
Immune-mediated nephritis occurred in 0.5% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.2%) [see Adverse Reactions (6.1)]. Nephritis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with nephritis, including 67% who received prednisone ≥40 mg per day or equivalent. Nephritis resolved in all patients.

Immune-Mediated Dermatomyositis
Immune-mediated dermatomyositis reactions, including erythema multiforme and pemphigoid, occurred in 1.7% of 534 patients receiving LIBTAYO, including Grade 3 (1.1%) and Grade 2 (0.6%) [see Adverse Reactions (6.1)]. In addition, SJS and TEN have been observed with LIBTAYO and with other products in this class. Systemic corticosteroids were required in all patients with dermatologic reactions, including 89% who received prednisone ≥40 mg per day or equivalent. Dermatologic reactions resolved in 35% of patients. Approximately 22% of patients had recurrence of dermatologic reactions after re-initiation of LIBTAYO.

Other Immune-Mediated Adverse Reactions
The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 534 patients who received LIBTAYO [see Adverse Reactions (6.1)] and 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.

Neurological Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome / myasthenia gravis, Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy
Cardiovascular Myocarditis, pericarditis, vasculitis
Diasperal 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 corticosteroids to reduce the risk of permanent visual impairment.

Gastrointestinal Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis Mucositis/keratitis and Conjunctive Tissue Mysitis, rhodanymosis and associated sequelae including renal failure, arthrites, polylymnia rheumatica
Hematological and Immunological Hemolitic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcodiosis, immune thrombocytopenic purpura, solid organ transplant rejection.
5.2 Infusion-Related Reactions

Severe (Grade 3 or 4) infusion-related reactions (IRRs) occurred in 0.2% of patients receiving LIBTAYO (see Adverse Reactions (6.1)). Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue LIBTAYO based on severity of reaction (see Dosage and Administration (2.2)).

5.3 Embryo-Fetal Toxicity

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential for a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose (see Use in Specific Populations (8.1, 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-Reactions (see Warnings and Precautions (5.2))

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared 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 in 534 patients in two open-label, single-arm, multicenter studies (Study 1423 and Study 1540), including 98 patients with metastatic (nodal or distant) CSCC, 65 patients with locally advanced CSCC, and 371 patients with other advanced solid tumors. LIBTAYO as a single agent or in combination with chemotherapy or radiation was administered intravenously at doses of 1 mg/kg every 2 weeks (n=27), 3 mg/kg every 2 weeks (n=446), 3 mg/kg every 3 weeks (n=12), 10 mg/kg every 2 weeks (n=8), 200 mg every 2 weeks (n=20) or 350 mg every 3 weeks (n=23). Among the 534 patients, 38% were exposed for ≤6 months and 16% were exposed for ≥12 months.

The data described below reflect exposure to LIBTAYO in 163 patients with advanced CSCC (metastatic or locally advanced disease) in Study 1423 and Study 1540. Patients received LIBTAYO 1 mg/kg every 2 weeks (n=1), 3 mg/kg every 2 weeks (n=139) or 350 mg every 3 weeks (n=23) as an intravenous infusion until disease progression, unacceptable toxicity, or completion of planned treatment. The median duration of exposure was 20 days (3-14 days).

The safety population characteristics were: median age of 71 years (38 to 96 years), 85% male, 96% white, and ECOG performance score (PS) of 0 (44%) or 1 (56%).

The most common adverse reactions reported in at least 20% of patients were fatigue, rash, and diarrhea. The most common Grade 3-4 adverse reactions (≥2%) were cellulitis, sepsis, hypertension, pneumonia, musculoskeletal pain, skin infection, urinary tract infection and fatigue. LIBTAYO was permanently discontinued due to adverse reactions in 5% of patients, adverse reactions resulting in permanent discontinuation were pneumonitis, autoimmune myocarditis, hepatitis, aspecific meningitis, complex regional pain syndrome, cough, and muscular weakness. Serious adverse reactions occurred in 28% of patients. Serious adverse reactions that occurred in at least 2% of patients were cellulitis, sepsis, pneumonia, pneumonitis and urinary tract infection.

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

Table 1: 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>N=163</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td></td>
<td>%</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash§</td>
<td>25</td>
<td>1.2</td>
</tr>
<tr>
<td>Pruritus§</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
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<td></td>
</tr>
<tr>
<td>Diarrhea§</td>
<td>22</td>
<td>0.6</td>
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§ Rash is a composite term that includes rash-maculopapular, rash, dermatitis, rash generalized, dermatitis herpetiformis, drug eruption, erythema, rash-urticarial, rash macular, rash papular, and skin reaction.

# Pruritus is a composite term that includes pruritus and pruritus allergic.

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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

6.2 Immunegeunicity

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

Anti-drug antibodies (ADA) were tested in 398 of 534 patients who received LIBTAYO and the incidence of cemiplimab-rwlc treatment-emergent ADAs was 1.3% using an electrochemiluminescent (ECL) bridging immunoenzymometric assay (EIAMA). 92% of persistent ADA responses were found in patients who developed anti-cemiplimab-rwlc antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab-rwlc.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. 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 malfomations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in P1- and P1-D1 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

Advise patients 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 163 patients with metastatic and locally advanced CSCC who received LIBTAYO in clinical studies, 72% were 65 years or older and 37% were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

17 PATIENT COUNSELING INFORMATION

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

Immun-Mediated Adverse Reactions

Advise patients that LIBTAYO can cause immune-mediated adverse reactions including the following (see Warnings and Precautions (5.1)):

- Pneumonitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of pneumonitis, including new or worsening symptoms of cough, chest pain, or shortness of breath.
- Colitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of colitis, including diarrhea, blood or mucus in stools, or severe abdominal pain.
- Hepatitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatitis.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophosphatia, or type 1 diabetes mellitus.
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.

Adjuvant Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately if they develop a new rash.

Infusion-Related Reactions

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

Embryo-Fetal Toxicity

Advise females of reproductive potential that LIBTAYO can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy (see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.2)).

Lactation

Advise female patients not to breastfeed while taking LIBTAYO and for at least 4 months after the last dose (see Use in Specific Populations (8.1, 8.2)).
**CONFERENCE COVERAGE: COA PAYER EXCHANGE SUMMIT 2019**

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**Providers Move Forward With 2-Sided Risk and Take on Pharma**

**HEADING INTO 2019**, the idea that oncology practices would embrace financial responsibility for clinical decisions struck many as far-fetched. Yet, when the time came to make the call, moving to 2-sided risk proved a “simple” decision, said Travis Brewer of Texas Oncology, who took part in a panel offering an update on the Oncology Care Model (OCM) at the start of the Community Oncology Alliance Payer Exchange Summit. The event took place October 28-29, 2019, in Tysons Corner, Virginia.

The invitation-only gathering of payers, providers, pharmaceutical leaders, and heads of employer coalitions—whose presence at the event has grown—was designed to focus squarely on payment reform in cancer care as community practices seek ways to stay independent amid competition from health systems.

Moderated by Basit Chaudhry, MD, PhD, of Tuple Health, the panel brought insights from both Brewer and Terrill Jordan of Regional Cancer Care Associates (RCCA), another large, multisite practice that decided to move forward with 2-sided risk before a December deadline imposed by CMS. The deadline, first set for October, called on practices in the OCM to take stock of where they are and move from so-called 1-sided risk—in which they share in savings gained from efficiencies—to 2-sided risk, taking on responsibility for total cost of care, subject to limits.

Jordan said the decision fit with both RCCA’s strategic mission and where the market was heading. The practice had taken on many other elements that affect cost, and the big one remaining was drug costs. “Two-sided risk was always looming,” he said. “Was this the right time?”

Brewer said many analyses went in Texas Oncology’s decision, which took effect July 1, but the process was similar. The practice had succeeded with clinical pathways and was seeing savings from the OCM performance periods, so moving to 2-sided risk seemed the next logical step.

Other payers, not just Medicare, would want 2-sided risk contracts, “It’s coming, and we need to be out in front of it,” Brewer said.

Jordan and Brewer discussed the importance of physician leadership, because oncologists stand to lose money out of pocket if practices don’t change. The process of getting to where RCCA’s oncologists are today, Jordan said, is “a journey in itself.”

“In 2012, if I had said, ‘We are going to 2-sided risk,’ I would not have a job,” he said. “Today I say, ‘We’re going to 2-sided risk,’ and they ask, ‘How?’”

Along the way, RCCA developed many strategies, and Chaudhry pressed Jordan to explain a tactic the practice calls “surrogate reporting.”

There is a long lag between actual episodes of care and when CMS returns data to practices, Jordan said, and RCCA realized at the outset that it needed to have a handle on where costs were accumulating and where resources had to be directed to keep patients out of the emergency department. That was a tall order, because RCCA’s internal systems was set up to handle claims, not make predictions.

The biggest change came in the way RCCA approaches its talks with drug makers. No longer content to wait for the payers to negotiate prices, Jordan said, the practice sat down to talk price directly with the drugmakers. Many are located in New Jersey, where RCCA has a huge footprint.

RCCA was blunt: “You don’t want to be on the list,” Jordan said. “Ultimately, we told the manufacturers, ‘You haven’t had to participate in risk…. You’re participating in risk through us now. If you’re not our partners, you’re our target.’”

Brewer agreed that the time for direct action has arrived. Based on his prior role on the payer side, he concluded that there are 3 types of people when it comes to value-based contracting: those willing to collaborate, those who will do it “kicking and screaming,” and those who “want no part of it,” he said.

“Those who absolutely no part of it are going to be standing out when the tornado hits,” Brewer said.

Chaudhry asked for more details on gaining physician buy-in. “You find that clinicians are more engaged,” Brewer said, describing Texas Oncology’s experience since the move to downside risk. “They’re all showing up to the meetings” on how this will be executed.

“What are the spirited conversations about?” Chaudhry asked.

Jordan offered examples, such as navigating which biosimilars are in which payer contracts, which gets very specific. “You’re messing with clinician time, and the currency of the clinician is their time,” he said. Any errors lead to a “hit to the pocketbook”: “This is something that hits to the very core of practice.”

Brewer agreed. “We can’t stock 4 different biosimilars for 4 different insurers. It doesn’t make sense financially,” he said. “If you’re going to trust us to take the risk, then you have to trust us to have a voice in these overall decisions.”

Chaudhry asked if either practice had dealt with reimbursement in the transition to 2-sided risk; neither had. The products are too new and not properly priced, Jordan said.

Where do value-based models go from here? There is considerable speculation—and concern—about what will happen when the OCM reaches the end of its 5-year run.

“Payer models have started to coalesce around something that looks like OCM,” Jordan said. He expects that CMS will continue to drive the direction of future value-based designs, and it will be hard for commercial payers to veer far from the Medicare model.

No matter what, Jordan said, the OCM has forever changed the landscape in decision making in cancer care: It assumes that the right place to make clinical decisions is at the level of the provider. “That’s fundamental,” he said.●

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**Pharma, Payers Must Unlock Key Data for Value-Based Agreements**

**IF VALUE-BASED AGREEMENTS** would help get the right drugs to the right patients, what is standing in the way?

Blame the struggle with value-based agreements on lack of access to data, say pharmaceutical leaders who participated in a discussion October 29, 2019, with Bo Gamble, director of Strategic Practice Initiatives for the Community Oncology Alliance (COA). The exchange took place at the group’s Payer Exchange Summit in Tysons Corner, Virginia.

Overcoming this barrier is critical if pharmaceutical manufacturers and providers are to collaborate directly on value-based agreements, which will be necessary as practices move to 2-sided risk under the Oncology Care Model (OCM) and any successor.

COA has submitted a model for federal review; dubbed OCM 2.0, it calls for these types of arrangements with 6 pharmaceutical manufacturers, including 4 who took part in the discussion: Merck, Janssen, Sanofi Genzyme, and Eli Lilly and Company (see Editor’s Note).

“Data is always a huge issue,” said Patrick Davish, executive director of Public Affairs and Policy at Merck. Historically, he said, value-based agreements have emerged between pharmaceutical manufacturers and payers, who tend to tightly control their claims data.

Until recently, Davish said, data sharing has been constrained by the Stark Law. Although CMS proposed changes that would ease limits on collaborating among many parts of the health system, manufacturers were left out of the reforms, “so the world has not changed in that respect,” he said.

HHS Secretary Alex Azar led Eli Lilly before returning to government, “[so he] knows we were excluded and did that deliberately,” Davish said. “We need to be better stewards of our reputation.”
Providers can help fill in the gaps, said Daniel Lyons, senior director of Value and Access at Sanofi Genzyme. “You have the electronic medical record at your fingertips.” Drug companies don’t have patient-level data and can struggle to learn how drugs work in combination, he said.

Robert Redman, senior marketing director for oncology at Eli Lilly, said manufacturers would welcome value-based agreements that are evidence based and driven by outcomes measures, whether that involves overall survival or progression-free survival. But in the absence of access to data, companies rely on surrogate measures, such as the number of cycles of therapy. “We’re trying to figure out innovative ways to do that,” he said.

Dimitry Gitarts of Janssen said manufacturers are willing to be innovative as providers take on more risk. For example, because dosing of oncology therapies is often based on patient weight, Gitarts said that if a practice has many patients who are overweight or very sick, those factors could be taken into account when developing agreements that focus on outcomes. “We can work on value-based agreements [that include] cost predictability,” he said.

Building agreements around the quality measures that community oncologists already gather every day makes sense, and reimbursement can follow, Gitarts said.

There are barriers to value-based agreements between payers and pharmaceutical manufacturers, but assuming these can be overcome, it is important to include patients in these agreements. When selecting therapies or deciding if biosimilars can be used, it is important that physicians have choices.

Gamble asked the group if it would be easier to do value-based agreements with the payer and provider together or just with the provider.

There are legal reasons to engage the payer, Davish said, and doing so at scale can help identify providers. In addition, the desire to develop the best contract may not be realized when dealing with a smaller entity. Gitarts agreed.

Assuming the barriers can be removed, it is important to include patients in agreements, according to Lyons: “They have a voice, as well.” When selecting therapies or deciding if a biosimilar will be used, “we do not want to restrict physician choice,” he said. “Not everyone wants to be forced to use something over something else.”

Gitarts asked where pharmaceutical manufacturers can share risk along with providers. Redman responded that this would come down to taking a look at drug improper usage and, if evidence calls for it, narrowing the label. Lyons said the OCM has shown that it’s all about using data to lower spending, and drugs are part of that. “If there’s a way to lower the spend on drugs by finding the right patients, we have to have access to the data,” he said.

This points to the need for diagnostic testing, especially for patients who have exhausted several treatment options, Gitarts said. Only patients who are eligible for treatments should get them, he told Gamble, adding, “This is the easiest of the questions you’ve asked.”

Gamble commented that the arrival of 2-sided risk may generate new discussions about the total cost of care, as it becomes necessary for providers to work with pharmaceutical manufacturers.

 Lyons encouraged the providers to help manufacturers avoid the soaring costs of data acquisition, and Redman said that better value-based solutions came down to “data and willingness”: It’s not uncommon to hear that reaching an agreement just isn’t worth all the effort, he said.

“Keep having conversations like this,” Gitart advised the physicians. Many things happening at the practice level take place beyond the reach of pharmaceutical companies, he said: “We can’t possibly know your patients to the extent that you do.”

EDITOR’S NOTE: On November 1, 2019, the Center for Medicare & Medicaid Innovation released a Request for Information for Oncology Care First, a successor model to the OCM (see Cover). In response, COA withdrew the OCM 2.0 model.

CMS’ Innovation Leader Touts Value of Physician Feedback

“ROBUST” FEEDBACK FROM PHYSICIANS has taken CMS’ Oncology Care Model (OCM) to the forefront of innovation, as the agency moves from fee-for-service to value-based reimbursement, according to a key adviser on the front lines of the shift.

During the Payer Exchange Summit in Tysons Corner, Virginia, Anand Shah, MD, a radiation oncologist who is senior medical adviser for innovation at CMS, expressed his appreciation for frontline oncologists’ role in the OCM’s success. He shared his thoughts with Ted Okon, MBA, executive director of the Community Oncology Alliance, during an October 29, 2019, conversation at the summit.

“A model is an assumption, so it’s never 100% perfect,” said Shah, who started out in the Center for Medicare and Medicaid Innovation (CMMI), the CMS entity that develops alternative payment models called for under the 2015 Medicare Access and CHIP Reauthorization Act of 2015 (MACRA).

“It is government, so oftentimes change is slow,” Shah said. But CMMI worked to incorporate the “physician voice” while balancing the need to conduct valid tests of different models, he said. Okon praised their efforts, adding, “Everyone knows I can be a little critical at times.”

The result, Okon said, is that OCM has done more than change reimbursement. Leaders of community practices have described fundamental changes in the way care is delivered, including greater focus on survivorship, stronger communication between physicians and patients, fewer hospitalizations, and better delivery of palliative care.

In some ways, Okon said, “it can’t be quantified, but it is very real.”

The multipayer OCM has reached a crossroads. The 175 practices taking part must decide by December if they want to move to 2-sided risk for the remaining time in the program, which ends in 2021. CMS held a “listening call” November 4, 2019, to plan for the successor to the OCM. As previously reported in Evidence-Based Oncology, feedback led to changes that summit attendees said made it easier for practices to move forward.1

The original decision point on 2-sided risk was set for this month; Okon gently pressed Shah for an additional extension to April to give practices more time to weigh the unknowns. Shah didn’t commit but noted that the OCM is a partnership between CMS and the practices. “It is an unknown for us, as well,” he said.

Okon and Shah also discussed the current debate around the radiation oncology model, which has been proposed as mandatory, to the dismay of leaders of the American Society for Radiation Oncology. Shah said this was a good example of where there has been “robust feedback.”

Reimbursement structures in radiation oncology differ from those in medical oncology, Shah noted, because of the capital investment required. That lead to the question “How do I deal with my capital in this model?”

Okon noted that, unlike medical oncology, radiation oncology had been “insulated” from payment reform until this proposal arose.
Areas for the Future

Shah expects to see more progress on multipayer alignment so that practices do not try to juggle multiple quality measures and requirements for different patients. In 5 to 10 years, he said, he hopes to see “1 set of incentives with no unintended consequences.”

Okon asked about the 2 big cost challenges in oncology: handling new therapies, especially gene-based therapies, and dealing with “the sickest of the sick,” who drive up costs not just in the OCM but across Medicare. “I don’t think any legislation can address that,” he said.

Shah noted the importance of this issue. “When we refer to ‘the sickest of the sick,’ we are working very actively both in primary care and in Medicare Advantage to see how we can provide these patients with the most intensive wraparound services,” he said. “How do we get these folks the care they need to keep them out of the emergency (department)?”

Okon said that addressing this group’s needs is critical not just from a cost perspective but also to improve quality of life: “When you talk about innovation, that’s something we really have to look at.”

REFERENCES


Broad Population Genetic Screening Faces Implementation Challenges

BROAD POPULATION-BASED GENOMIC screening has the potential to improve patient care by detecting genetic causes of diseases before they occur; however, the economics behind this approach have not been fully validated, according to a session on the clinical and economic utility of whole-genome sequencing (WGS) at the Academy of Managed Care Pharmacy Nexus 2019 meeting, held October 29 to November 1, 2019, in National Harbor, Maryland.

“We don’t really have very many good models out there now that are looking at the cost-effectiveness. We do need to quantify the costs, but doing so is complicated,” said Laney Jones, PharmD, MPH, assistant professor at the Geisinger Center for Pharmacy Innovation and Outcomes, during the presentation. “The personal utility of genomic knowledge is often missing from these current models.”

The current methods for genetic testing include chromosomal microarray (CMA), which is designed to detect copy number variations and gene duplications and deletions. Broader testing techniques include whole-exome sequencing (WES) and WGS. In addition to deletions and insertions, WES, which focuses on 1% to 2% of the entire genome that contains 85% of the genes related to hereditary diseases, can also identify missense, nonsense, and splice site mutations. The broadest approach, WGS, covers DNA variations that can affect gene activity.

“There are 5200 genetic disorders for which the molecular basis is known,” said Lon Castle, MD, chief of lab and specialty drug services at eviCore health.

Findings from a randomized pilot study looking at short-term costs between WGS and WES, with results received for 527. Of those tested, 527 were negative and 14 tested positive (2.6% yield).

“We’re looking to anticipate care for disease prevention instead of reacting once someone has a disease,” said Jones. “This strategy allows us to do earlier detection of disease and enables better management and improved outcomes. This provides more reliable identification of the risk of disease for patients and their families.”

Drawbacks and Costs

Some of the drawbacks of population screening are scalability and the costs associated with testing, Jones noted. Reimbursement from insurance companies is still very guideline specific, and genomic testing is not yet fully integrated into electronic health records. Chief among these challenges are costs, as most economic models are focused on drugs and not diagnostics.

The direct costs associated with population screening are for the assays, the analysis, and the return of the results. Potential downstream costs exist for provider and patient education, confirmation testing, and interventions and surveillance. Population screening might accrue other ancillary costs, including those for false reassurances, interventions or surveillance in response to false positives, and the effects on insurance or employment.

Findings from a randomized pilot study looking at short-term costs between family history alone or WGS were published in 2018. In a cardiology setting, WGS cost $5098 more than family history alone. A $5073 difference was noted in the primary care setting. The downstream costs did not differ significantly between groups.

“We don’t always know the prevalence of genomic conditions in unselected populations, especially in fields like familial hypercholesterolemia. These markers are always changing, and how we define these diseases is changing.”

Geisinger Experience With Population Screening

The Geisinger hospital network launched a broad population-level genetic screening program labeled MyCode in 2007. The hospital system, which is located in central Pennsylvania, has 2800 providers and 1.5 million active patients across 13 campuses. Tied to this, from a payment perspective, the Geisinger health plan has over 580,000 members and covered approximately 40% of those in the MyCode project.

Overall, 253,108 patients participated in the MyCode project, with samples provided for 172,819. Of these, 64,309 were analyzed, with clinical results reported for 1068. The majority of these patients were of European ancestry (97%) with a median age of 59.21 years. The project looked specifically at the diseases indicated as tier 1 for genomic application by the CDC: hereditary breast and ovarian cancer (HBOC) syndrome, Lynch syndrome, and familial hypercholesterolemia. These conditions are expected in 1 in 400, 1 in 440, and 1 in 250 individuals, respectively.

Overall, BRCA1/2 mutations were found in 290 of these participants (27%), indicating HBOC. One hundred twenty-five (12%) had APOB or LDLR gene alterations, indicating familial hypercholesterolemia, leading to early-onset coronary artery disease and stroke. An additional 101 patients (9%) tested positive for Lynch syndrome, indicating the potential for early colon, uterine, and other cancers.

Of those detected, 42% did not have any evidence of a personal history of cancer and 50% did not have any evidence of a family history of cancer, suggesting that current screening methods would have missed these patients. Two-thirds of the detected individuals (68%) were eligible for risk management.

Not only did the detection of hereditary risk affect the individual who was tested, but it also had implications for the rest of the family members who did not previously have a known family history of cancer. Findings from the Geisinger project aligned closely with previously reported results from JAMA, which showed that 55% of those identified by population screening did not meet the criteria for indication-based testing, according to National Comprehensive Cancer Network (NCCN) guidelines.

“From this initial report and through our primary care docs and other providers in our system learning more about the MyCode project and its implications to clinical care, they’ve really pushed for the translation of this research project to be transitioned to clinical care,” said Jones. Following this push, population-based genomic screening was incorporated into 2 Geisinger clinics. As of August 2019, 679 patients had consented to the testing, with results received for 527. Of those tested, 527 were negative and 14 tested positive (2.6% yield).

“From this initial report and through our primary care docs and other providers in our system learning more about the MyCode project and its implications to clinical care, they’ve really pushed for the translation of this research project to be transitioned to clinical care,” said Jones. Following this push, population-based genomic screening was incorporated into 2 Geisinger clinics. As of August 2019, 679 patients had consented to the testing, with results received for 527. Of those tested, 527 were negative and 14 tested positive (2.6% yield).

“We’re looking to anticipate care for disease prevention instead of reacting once someone has a disease,” said Jones. “This strategy allows us to do earlier detection of disease and enables better management and improved outcomes. This provides more reliable identification of the risk of disease for patients and their families.”
said Jones. “We also don’t always know the penetrance of the genomic condition or the effectiveness in presymptomatic interventions.”

Adding to the complexity of reimbursement is the lack of a single governing entity that is responsible for payment decisions in the genetic testing space. For medications, FDA approval is typically sufficient for payers to make a coverage decision.

“In the payer world, CMS decides if they’ll pay or not pay for a genetic test, but that’s only for the Medicare population, and that has no bearing on what commercial entities do,” said Castle. “CMS is looking at a biased population, as individuals over 65, some tests work well in that population and some do not. That is why payers do not blindly follow CMS like some follow the FDA. It’s not as clear of a picture.”

Rather than acting as one overarching group to weigh in on payment decisions, the ACCC model has been developed by the CDC to assess new molecular diagnostic, genomic tests and technologies in an evidence-based fashion, according to Castle. For the model, the framework assesses analytic validity, clinical validity, clinical utility, and ethical, legal, and social implications. Coverage decisions are based largely on the first 2 aspects, he noted.

Other sources of potential payment decisions for genetic testing come from guidelines or pathway organizations, technology assessment committees, regulatory and other governmental agencies, professional societies, and individually contracted providers and industry experts. The key for each of these, however, is to understand how their recommendations are reached. For instance, Castle noted that NCCN is not evidence based but is consensus based, which is an important distinction.

**Improving WGS Diagnostic Yield**

Evidence on the effectiveness of WGS has not yet been strong enough to support broad payer acceptance. Moreover, challenges still remain for interpretation of the data. The NTRK gene is an example of the complexity of interpretation, Castle noted. The treatments larotrectinib (Vitrakvi) and entrectinib (Rozlytrek) are approved for patients with an NTRK gene fusion, which is significantly different from an NTRK gene mutation.

At this time, WES remains significantly cheaper and faster than WGS, further complicating the payment decision. Additionally, in a large meta-analysis, the diagnostic yield was not significantly different between WGS and WES. In the analysis, which looked at 20,968 children across 37 studies, WGS had a diagnostic yield of 41%, whereas WES had a yield of 36%. Both provided a significantly higher yield than CMA (10% yield).

“There’s a lot of this we still need to figure out how to handle as a healthcare community. There are all sorts of informed-consent issues that we need to grapple with,” said Castle. “There are a lot of things to think about with WGS, other than just the technology and validity of the tests.”

As the price of WGS continues to decline, investigators are working to refine the diagnostic yield. Narrowing the focus of studies to more clearly defined genetic causes could help elevate the yield, Castle said. As an example, he cited findings from a study looking at 103 children with phenotypes suggesting a genetic cause for their disease. In this analysis, the diagnostic yield with WGS was 41%. The authors of the paper noted that 18 new diagnoses were made in the study based on variants detected by WGS that were not detectable by WES.

“This is how we can get this testing done, if you limit it to where it is going to be the most helpful for the largest segment of the population. That’s who you want to test. Other people, perhaps, based on appeals, but that’s not where we should start out of the gate. We aren’t going to start with everybody,” said Castle.

**References**


**Preparing for the Near-Term Pipeline of Therapies and Opportunities for Cost Savings**

**INCREASED COMPETITION IS MAKING** its way into the specialty drug market, affecting orphan conditions, cancer types, and even common specialty conditions, and is presenting some cost savings opportunities, explained Aimee Tharaldson, PharmD, senior clinical consultant for emerging therapeutics at Express Scripts, who presented on the specialty pharmaceutical pipeline during her regular session at the Academy of Managed Care Pharmacy Nexus 2019 meeting.

Several specialty drugs will be going generic over the next few years, with a $34 billion market opportunity for first-time generics for specialty medications over the next 4 years, Tharaldson explained. Generics are expected beginning in September 2020 for the multiple sclerosis drug Tecfidera, which has annual sales of about $3.5 million. At the same time, the market will see first-time generics for Truvada, the pre-exposure prophylaxis for HIV, which has annual sales of about $3 billion.

**Biosimilars**

Much activity around competition is happening in the biosimilar space. Seventy-seven patents are set to expire through 2023, and biosimilars have a $62 billion opportunity over the next 4 years. However, the US market is moving slowly. For instance, Tharaldson noted that expectations of 2019 biosimilar launches were optimistic—Enbrel biosimilars now may not launch until 2029. Although 29 biosimilars are approved for 8 biologics in the United States, only 9 biosimilars for 6 biologics have actually launched:

- Filgrastim biosimilars: Zarxio has gained 17% of the market share, and Nivestym has 34% of the market.
- Infliximab biosimilars: The reference product, Remicade, still has 92% of the market share, so these biosimilars have had a more difficult time gaining share.
- Avastin biosimilars: The 1 launched biosimilar has provided a 15% discount off the reference drug’s list price.
- Herceptin biosimilars: The 1 launched biosimilar has also provided a 15% discount to the reference drug’s list price.

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**CONFERENCE COVERAGE: AMCP NEXUS 2019**
• Epogen/Procrit biosimilar: Retacrit has about 22% of the market.
• Neulasta biosimilars: The biosimilars Udenyca and Fulphila have only about 18% of the market, but they are priced at more than a 25% discount off Neulasta.

Products may not have launched yet for a variety of reasons, including patent protections, patent litigation, and simply the decision not to launch, according to Tharaldson. She discussed 3 biosimilars with pending approval, of which 2 have since been approved. One of them, Pfizer’s Humira biosimilar, will not launch until 2023.

Currently, biosimilars are acting as a competing brand class. Tharaldson noted that biosimilar manufacturers face many legal hurdles, and once their agent makes it to market, they are having a difficult time capturing that market.

“But eventually [they] are going to lead to significant cost savings,” Tharaldson said. “So in just a little over 3 years, we’re going to have multiple biosimilars to Humira, which is an $18 billion-per-year drug, so that’s going to help lower spend in many therapy classes.”

Cancer

Although 1.7 million new cases of cancer are diagnosed each year, the death rate has dropped 25% since 1991. However, approvals saw a big dip, with only 8 so far in 2019 compared with 17 novel cancer drug approvals in 2018.

More than 100 types of cancer have been identified, with breast cancer being the most common in women and prostate cancer being the most common in men. Of the cancer drugs in the pipeline pending approval, 4 are breakthrough therapies:

• Avapritinib, an oral kinase inhibitor to treat PDGFRA exon 18 mutation in gastrointestinal stromal tumors. In addition to being approved for patients with the mutation, the agent could be granted a second indication for fourth-line use after other options.
• Zanubrutinib, a Bruton tyrosine kinase inhibitor to treat relapsed/refractory mantle cell lymphoma in patients who progressed on other therapies
• Enfortumab vedotin, an antibody-drug conjugate targeting Nectin-4, to be used as a third-line treatment in advanced urothelial cancer. The early data showed a 44% overall response rate, although 12% of patients discontinued therapy because of adverse events.
• Trastuzumab deruxtecan, an antibody-drug conjugate targeting HER2 in patients with HER2-positive metastatic breast cancer who had previously been treated with at least 2 previous anti-HER2 therapies. Investigators are also evaluating it for other HER2 cancers, like gastric, lung, and colon cancers.

Eight breakthrough therapies are in the near-term pipeline, including 2 chimeric antigen receptor (CAR) T-cell therapies: idecabtagene vilocilucel from bluebird bio to treat multiple myeloma and lisocabtagene maraleucel from Celgene to treat diffuse large B-cell lymphoma.

Gene Therapies

More than 600 cell and gene therapies are in the pipeline. These therapies modify a person’s genes by replacing disease-causing genes, inactivating disease-causing genes, or introducing new or modified genes.

Currently only 6 are approved: 4 immunotherapies (2 of which are CAR T-cell therapies) and 2 gene replacement therapies. Another 9 could be approved in the next year, including 4 cancer immunotherapies, 3 gene replacements for rare conditions, and 2 gene replacements for hemophilia.

Nonalcoholic Steatohepatitis

3 of these drugs to treat nonalcoholic steatohepatitis (NASH) are in the near-term pipeline, only 1 of which is currently pending approval. Patients with NASH have fat in the liver, liver inflammation, and liver damage. It is the fastest-growing cause of liver cancer and transplant, and an estimated 6 million to 16 million Americans have NASH. These patients also tend to have other comorbidities, such as high cholesterol, type 2 diabetes, insulin resistance, and obesity.

“‘There’s nothing specifically approved to treat these patients,’ Tharaldson said. ‘They just need to lose weight and eat healthy and exercise and avoid alcohol.’

Most of the drugs in development for NASH have different mechanisms, and the standard of care will likely be some kind of combination therapy, Tharaldson noted.

Obeticholic acid is the drug expected to receive approval first, in May 2020. Results of one study showed that it improved liver fibrosis with no worsening of NASH in 23% of patients versus 12% in the placebo group. It is currently on the market with a $70,000 annual price tag to treat a rare condition; NASH affects a much larger patient population, so “it’s going to be interesting to see how this is priced,” Tharaldson said.

Other drugs to treat NASH will come out later. The next treatment may be approved in late 2020, but phase 3 data have not been released. Another 3 drugs may follow in 2021, with potentially 5 in 2022 or later.

The NASH market has the potential to be quite large, Tharaldson said, with costs of $20 billion or more a year. However, a lot of unknowns still remain, and positive phase 3 data have been scant. In addition, methods other than liver biopsy, which is expensive and invasive, are needed to identify patients with NASH.

Finally, cost is a big unknown. Some estimates have put these therapies in the $3000-to-$6000 range, similar to a statin or a diabetes medication, but other estimates place the cost of these therapies much higher, at $70,000 a year.

Data Collaborations Drive Advances in the Use of Real-World Evidence

THE NUMBER OF EXPEDITED FDA approvals for cancer drugs that are based on surrogate end points is increasing, leading many to search for new ways to uncover efficacy and safety data to justify the costs associated with these treatments. With the growth of data innovations and collaborations, the answer might be found in real-world evidence (RWE), according to presentations at the 9th Annual Research Symposium held in conjunction with the Academy of Managed Care Pharmacy Nexus 2019 meeting.

“We can’t expect this to directly replicate clinical research, but it’s really important to advance this methodology,” said Jeff Allen, PhD, president and chief executive officer of Friends of Cancer Research (FOCR), a group that was instrumental in the development of the breakthrough therapy designation. “If we’re going to get back to the idea of how we’re going to expedite the development of treatments for patients who have no other therapeutic options, but also carry out the responsibility to continue to evaluate the effect of these therapies and benefits over time, this is a way to advance that need in a different way.”

Since the launch of the breakthrough designation in 2012, the FDA has approved 150 breakthrough therapies and granted more than 332 breakthrough therapy designations, according to FOCR. In an analysis of the impact of the breakthrough program conducted in 2016, the designation was found to accelerate premarket drug development by 2.2 years, representing a significant trend toward rapid access to potentially lifesaving medications.

However, this new paradigm for drug approval has generated controversy because a majority of the regulatory decisions under the program are based on surrogate end points and not on overall survival (OS). Although OS is the gold standard, many challenges make it difficult to achieve, even in large, randomized phase 3 trials, Allen noted. In general, crossover between arms commonly confounds the calculation of OS, and in some cases, the amount of time needed to show a statistical benefit is simply too long.

RWE has the potential to overcome these challenges, Allen noted, and FOCR has teamed up with several data partners, including the American Society of Clinical Oncology (ASCO CancerLinQ), Cota, and Flatiron Health, to conduct a pilot study to determine exactly how it can help. The analysis has shown that
patients in the real-world setting were older than their randomized controlled trial counterparts and that data collected in the pilot study could be used for comparisons across treatment groups for several efficacy end points.

Through the collaboration, clinical end points like progression-free survival (PFS), time to next treatment, and time to discontinuation could be tracked in a patient population that closely mirrored that in a true treatment setting, Allen said. Many of these end points correlated with OS; however, survival itself still remained challenging to calculate, as the date of death is not always available, he added.

“What we were able to see, at least from the initial partners who did this analysis for us, is that they were able to construct, with great detail, the different characteristics of the populations who were receiving each product,” Allen said. “They were also able to show that some of these nontraditional measures, like time to treatment discontinuation, actually correlated quite well with traditional measures, like overall survival.”

NCI Looks to Partnerships to Advance Cancer Surveillance

The Surveillance, Epidemiology, and End Results (SEER) Program, which the National Cancer Institute (NCI) has funded since 1973, houses real-world data for 34% of the US population. Although the registry has traditionally had several limitations, the NCI is looking to expand the reach of the database through partnerships, according to Donna Rivera, PharmD, MSc, a scientific project officer at the NCI.

“The main goal for the enhancement is to create a system that represents population-level, real-world data to supplement clinical trials and understand the effectiveness of oncology care outside the clinical setting. Clinical trials represent 3% to 5% of the adult oncology population. However, that leaves 95% of the population outside of clinical trials, for which we need quality data.”

—Donna Rivera, PharmD, MSc, National Cancer Institute

Through these partnerships, the NCI is looking to add data on comorbidities, adverse drug events, treatment success, second and third courses of treatment, and health outcomes such as survival. SEER has traditionally collected only diagnosis, staging information, tumor characterization, and initial course of treatment.

“The main goal for the enhancement is to create a system that represents population-level, real-world data to supplement clinical trials and understand the effectiveness of oncology care outside the clinical setting,” said Rivera. “Clinical trials represent 3% to 5% of the adult oncology population. However, that leaves 95% of patients outside of clinical trials, for which we need quality data.”

The new initiative looks to add further biomarkers through partnerships with Genomic Health and Myriad/Invitae. Additionally, partnerships with CVS and Walgreens will provide data on outpatient prescription use for oral medications, with the ability to measure not only utilization but also adherence. The collaboration will also tap into electronic health records (EHRs) through the CancerLinQ program and will include information on radiation oncology through partnerships with Varian/Elekta.

As an example of a recent approval that could benefit from additional RWE, Rivera discussed the tumor-agnostic indication for larotrectinib (Vitrakvi), which was a first for the FDA. The approval for larotrectinib, which arrived in November 2018, was based on objective response rates (ORRs) across 3 early-phase clinical trials that enrolled 55 adult and pediatric patients with a variety of TRK fusion-positive cancers. In the studies, the ORR was 75% across groups by independent review.1 RWE could be used to provide further insight into the treatment, she said.

“The changing landscape of cancer treatment includes rapid drug development,” said Rivera. “We need to be able to understand these new medications being approved, especially within the context of genomic testing, the integration of diagnostics testing into patient treatment, and increased survivorship.”

Once fully in place, the enhanced SEER database will become a tool for monitoring a variety of factors, down to the most common medications prescribed for a given type of cancer by region. Additionally, the registry will hold ample data to allow for trend analyses, monitoring of patient adherence, clinical outcomes, and differences in use across subpopulations, Rivera noted.

“Pharmacists and healthcare providers now have a resultant education requisite to learn data science awareness as an integral aspect of clinical practice in the era of big data,” said Rivera. “As data [shape] evidence-based care, pharmacists with clinical data science awareness can expand their role as collaborators on the interdisciplinary team. Collaboration in the data science and real-world evidence space is absolutely essential.”

FDA Adds Perspective

Examples of the FDA’s feelings about RWE are starting to emerge. In April 2019, the agency approved the cyclin-dependent kinase 4/6 inhibitor palbociclib (Ibrance) in combination with endocrine therapy for the treatment of men with hormone receptor–positive, HER2-negative advanced or metastatic breast cancer, based on an assessment of additional clinical data and findings from EHRs and IQVIA.

Despite that step in the direction of incorporating RWE into a regulatory decision, Harpreet Singh, MD, of the FDA, noted that the decision was based primarily on clinical data and not on the data from the EHRs or IQVIA. She highlighted several of the drawbacks inherent in currently available RWE, including a lack of full data on clinical outcomes like PFS and OS, further emphasizing the need for new models built on collaboration.

“The rationale for why we felt we were able to extrapolate and expand the indication for palbociclib to include male patients was largely based on the registration trials, PALOMA-2 and -3. We found the real-world evidence to be supportive but not driving our decision,” said Singh, team leader for Breast Cancer Drug Development at the FDA. “It didn’t tell us anything [different] from what we would have otherwise expected. There are well-characterized safety profiles for this drug. There were no new safety signals.”

The use of RWE in regulatory decisions still has far to go, but efforts from FOCR and the NCI are steps in adding to the data more clinical meaning, which is currently based largely on claims data.

“Because of the limitations in real-world evidence, our solution at the agency is to ask sponsors to include patients in their prospective clinical trials,” said Singh. “There is potential for more use of real-world evidence. We’re not stopping, but in this 1 example, there certainly were limitations.”

REFERENCES


An FDA label change causes immunotherapy prescriptions for bladder cancer to decline

Read more at: onclive.com/link/6800

CONFEERENCE COVERAGE: AMCP NEXUS 2019
Here for HER too™

Introducing Ogivri™, the first FDA-approved biosimilar to Herceptin® (trastuzumab) based on totality of evidence and the first with OS data at 36 months⁴

Primary endpoint met: equivalent ORR at 24 weeks compared with Herceptin⁴

Important Safety Information:

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

Cardiomyopathy:
Administration of trastuzumab products can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving trastuzumab with anthracycline-containing chemotherapy regimens. Evaluate left ventricular function in all patients prior to and during treatment with Ogivri. Discontinue Ogivri treatment in patients receiving adjuvant therapy and withhold Ogivri in patients with metastatic disease for clinically significant decrease in left ventricular function.

Infusion Reactions: Pulmonary Toxicity:
Administration of trastuzumab products can result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of administration. Interrupt Ogivri infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue Ogivri for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.

Embryo-Fetal Toxicity:
Exposure to trastuzumab products during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception.

Indications and Usage:

Adjuvant Breast Cancer
Ogivri is indicated for adjuvant treatment of HER2-overexpressing node-positive or node-negative (ER/PR-negative or with one high-risk feature*) breast cancer:
- As part of a treatment regimen containing doxorubicin, cyclophosphamide and either paclitaxel or docetaxel
- With docetaxel and carboplatin
- As a single agent following multi-modality anthracycline-based therapy

Select patients for therapy based on an FDA-approved companion diagnostic for Ogivri.

* High-risk defined as ER/PR positive with one of the following features: tumor size >2 cm, age <35 years, or tumor grade 2 or 3.

Metastatic Breast Cancer
Ogivri is indicated:
- In combination with paclitaxel for the first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

Select patients for therapy based on an FDA-approved companion diagnostic for Ogivri.

Important Safety Information:

Cardiomyopathy
- Ogivri administration can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving trastuzumab with anthracycline-containing chemotherapy regimens
- Trastuzumab products can cause left ventricular cardiac dysfunction, arrhythmias, hypertension,

Disabling cardiac failure, cardiomyopathy, and cardiac death. Trastuzumab products can also cause asymptomatic decline in left ventricular ejection fraction (LVEF). Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan

* Evaluate left ventricular function in all patients prior to and during treatment with Ogivri
* Discontinue Ogivri treatment in patients receiving adjuvant therapy and withhold Ogivri in patients with metastatic disease for clinically significant decrease in left ventricular function

OS: Overall survival ORR: Overall response rate
Confirmed biosimilarity based upon the totality of evidence

Demonstrated equivalence when compared to Herceptin in efficacy and safety in the phase 3 HERITAGE trial of patients with HER2+ metastatic breast cancer.

Offers similar patient access support through Mylan ADVOCATE® for seamless transition to Ogivri

Delivers the promise of greater access to patients

Please see the brief summary of the full Prescribing Information for Ogivri on the following pages.

Important Safety Information: (continued)

Infusion Reactions
- Ogivri administration can result in serious and fatal infusion reactions
- Symptoms usually occur during or within 24 hours of Ogivri administration
- Interrupt Ogivri infusion for dyspnea or clinically significant hypotension
- Monitor patients until symptoms completely resolve
- Discontinue Ogivri for infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. Strongly consider permanent discontinuation in all patients with severe infusion reactions
- Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion include nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia

Embryofetal Toxicity
- Exposure to Ogivri during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception
- Verify the pregnancy status of females of reproductive potential prior to the initiation of Ogivri
- Advise pregnant women and females of reproductive potential that exposure to Ogivri during pregnancy or within 7 months prior to conception can result in fetal harm
- Advise females of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose of Ogivri. Advise female patients to contact their healthcare provider with a known or suspected pregnancy
- Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for Ogivri treatment and any potential adverse effects on the breastfed child from Ogivri or from the underlying maternal condition

Pulmonary Toxicity
- Ogivri administration can result in serious and fatal pulmonary toxicity, which includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, noncardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions
- Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity
- Discontinue Ogivri in patients experiencing pulmonary toxicity
- Exacerbation of Chemotherapy-Induced Neutropenia
- In randomized, controlled clinical trials, the per-patient incidences of N3-CTC Grade 3-4 neutropenia and of febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was similar among patients who received trastuzumab and those who did not

Most Common Adverse Reactions
- The most common adverse reactions associated with trastuzumab in breast cancer are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia
- The most common adverse reactions associated with trastuzumab in metastatic gastric cancer are neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia

Patients in >40 countries have been treated with formulations of Mylan’s biosimilar trastuzumab.

**Indications and Usage**

**Adjuvant Breast Cancer**

Ogivri is indicated for adjuvant treatment of HER2-overexpressing node-positive or node-negative breast cancer (see Clinical Studies) - breast cancer

- A part of the treatment regimen consisting of doxorubicin, cyclophosphamide, and paclitaxel (platinelose) in addition to the above regimen.
- A part of the treatment regimen consisting of doxorubicin, paclitaxel, and carboplatin.

**Metastatic Breast Cancer**

Ogivri is indicated for:

- An adjuvant or neoadjuvant setting.
- A part of the treatment regimen consisting of doxorubicin, paclitaxel, and carboplatin.

**Cardiomyopathy**

Trastuzumab products can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death (see Banned Warning: Cardiomyopathy). Trastuzumab products can also cause asymptomatic decline in left ventricular function with increased risk of congestive heart failure in patients receiving trastuzumab. Ogivri patients may have a higher risk of myocardial dysfunction, and patients receiving Ogivri should be closely monitored for cardiac events.

**Contraindications**

None.

**Warnings and Precautions**

Cardiomyopathy

Trastuzumab products can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death. Ogivri patients may have a higher risk of myocardial dysfunction, and patients receiving Ogivri should be closely monitored for cardiac events.

**Cardiac Monitoring**

Conduct thorough cardiac assessment, including electrocardiogram and physical examination, and determine of Ogivri by echocardiogram or MUGA scan. The following should be performed:

- Baseline LVEF measurement immediately prior to initiation of Ogivri.
- LVEF measurements every 3 months during and upon completion of Ogivri.

**Infusion Reactions**

Infection reactions can be severe and include: sepsis, fever, chills, hypotension, nausea, vomiting, diarrhea, rash, urticaria, anaphylaxis, and angioedema. Ogivri patients may experience refractory anaphylaxis after receiving Ogivri. Ogivri patients should be closely monitored for cardiac events.

**Cardiac dysfunction**

Cardiac dysfunction can occur in Ogivri patients and should be monitored closely. Ogivri patients may develop symptomatic cardiac dysfunction or an asymptomatic decline in left ventricular function with increased risk of congestive heart failure.

**Precautions**

- Baseline LVEF measurement should be performed before Ogivri.
- LVEF measurements should be performed every 3 months during and upon completion of Ogivri.

**Post-infusion effects**

Post-infusion reactions can be severe and include: fever, chills, hypotension, nausea, vomiting, diarrhea, rash, urticaria, anaphylaxis, and angioedema. Ogivri patients should be monitored closely for cardiac events.

**Contraindications**

None.

**Warnings and Precautions**

Cardiomyopathy

Trastuzumab products can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death. Ogivri patients may have a higher risk of myocardial dysfunction, and patients receiving Ogivri should be closely monitored for cardiac events.

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- LVEF measurements should be performed every 3 months during and upon completion of Ogivri.

**Post-infusion effects**

Post-infusion reactions can be severe and include: fever, chills, hypotension, nausea, vomiting, diarrhea, rash, urticaria, anaphylaxis, and angioedema. Ogivri patients should be monitored closely for cardiac events.
higher level grouping term.

In Study 1, a comparison of 3-weekly trastuzumab treatment for two years versus one year was also performed. The rate of asymptomatic cardiac dysfunction was increased in the 2-year trastuzumab treatment (3.1%) vs. 1.4% in the one-year trastuzumab treatment arm. More patients experienced at least one adverse reaction of Grade 3 or higher in the 2-year trastuzumab treatment arm (20.4%) compared with the one-year trastuzumab treatment arm (16.3%).

The safety data from Studies 1 and 2 were obtained from 1,655 patients, all of whom received trastuzumab; the median treatment duration was 51 weeks. The median age was 49 years (range 24 to 80); 84% of patients were White, 7% black, 4% Hispanic, and 1% Asian.

Table 3: Adverse Reactions for Study 3, All Grades

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>One Year Trastuzumab (n = 1678)</th>
<th>Observation (n = 1708)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>64 (4%)</td>
<td>35 (2%)</td>
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<tr>
<td>Diarrhea</td>
<td>60 (4%)</td>
<td>29 (2%)</td>
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<tr>
<td>Infection F. Decreased</td>
<td>58 (3.5%)</td>
<td>11 (0.6%)</td>
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<tr>
<td>Palpitations</td>
<td>48 (3%)</td>
<td>12 (0.7%)</td>
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<tr>
<td>Cardiac Arrhythmiasa</td>
<td>40 (2.5%)</td>
<td>17 (1%)</td>
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<tr>
<td>Cardiac Failure</td>
<td>30 (2%)</td>
<td>5 (0.3%)</td>
</tr>
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<td>Cardiac Disorder</td>
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</tr>
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<td>Ventricular Dysfunction</td>
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<td>0 (0.0%)</td>
</tr>
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<td>Respiratory Therapeutic Monitoring Disorder</td>
<td>4 (0.2%)</td>
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<tr>
<td>Cough</td>
<td>81 (5%)</td>
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<td>Influenza</td>
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<td>Dyspnea</td>
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<td>URI</td>
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<td>Rhinitis</td>
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<td>Pharyngodyngia Pain</td>
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<td>Intestinal Pneumonitis</td>
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<td>0 (0.0%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>123 (7%)</td>
<td>16 (1%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>123 (7%)</td>
<td>16 (1%)</td>
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<tr>
<td>Nausea</td>
<td>108 (6%)</td>
<td>19 (1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>58 (3.5%)</td>
<td>10 (0.6%)</td>
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<td>Constipation</td>
<td>33 (2%)</td>
<td>17 (1%)</td>
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<tr>
<td>Dyspepsia</td>
<td>30 (2%)</td>
<td>9 (0.5%)</td>
</tr>
<tr>
<td>Upper Abdominal Pain</td>
<td>29 (1%)</td>
<td>15 (1%)</td>
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<tr>
<td>Macrovascular and Connective tissue disorders</td>
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<tr>
<td>Arthritis</td>
<td>1.37 (8%)</td>
<td>9.8 (6%)</td>
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<tr>
<td>Back Pain</td>
<td>91 (6%)</td>
<td>58 (3%)</td>
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<td>Myalgia</td>
<td>63 (4%)</td>
<td>17 (1%)</td>
</tr>
<tr>
<td>Bone Pain</td>
<td>49 (3%)</td>
<td>26 (2%)</td>
</tr>
<tr>
<td>Muscle Spasm</td>
<td>46 (3%)</td>
<td>0.2%</td>
</tr>
<tr>
<td>Neurovascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>162 (70%)</td>
<td>49 (3%)</td>
</tr>
<tr>
<td>Farsightedness</td>
<td>29 (2%)</td>
<td>11 (0.6%)</td>
</tr>
<tr>
<td>Skin &amp; Subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>70 (4%)</td>
<td>10.6%</td>
</tr>
<tr>
<td>Nail Disorders</td>
<td>43 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>40 (2.5%)</td>
<td>10.6%</td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>100 (6%)</td>
<td>6 (0.4%)</td>
</tr>
<tr>
<td>Edema Peripheral</td>
<td>79 (5%)</td>
<td>37 (2.2%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>85 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Neurological Illness</td>
<td>7 (4.5%)</td>
<td>30 (2%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>40 (2.5%)</td>
<td>3 (0.2%)</td>
</tr>
<tr>
<td>Infections</td>
<td>1 (0.06%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>135 (8%)</td>
<td>0.5%</td>
</tr>
<tr>
<td>UTI</td>
<td>39 (2.5%)</td>
<td>0.0%</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1.0 (0.6%)</td>
<td>10.6%</td>
</tr>
<tr>
<td>Autoimmune Inflammatory</td>
<td>4 (0.3%)</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

*Median follow-up duration of 12.6 months in the one-year trastuzumab treatment arm. The incidence of Grade 3 or higher adverse reactions was <1% in both arms for each listed term.
Table 5: Study 7: Per-Patient Incidence of Adverse Reactions of All Grades Incidence > 1% (Incidence > 1% Between Arms) and Higher Incidence in Trastuzumab Arm

<table>
<thead>
<tr>
<th>Body System/Adverse Event</th>
<th>AC (n = 1170)</th>
<th>Trastuzumab (n = 1878)</th>
<th>Observation (n = 1708)</th>
<th>AC (n = 1052)</th>
<th>Trastuzumab (n = 1682)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (15%)</td>
<td>24 (21%)</td>
<td>27 (23%)</td>
<td>15 (14%)</td>
<td>23 (21%)</td>
</tr>
<tr>
<td>WBC Count</td>
<td>10 (9%)</td>
<td>16 (14%)</td>
<td>13 (11%)</td>
<td>10 (9%)</td>
<td>15 (13%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (6%)</td>
<td>18 (15%)</td>
<td>12 (11%)</td>
<td>6 (6%)</td>
<td>18 (15%)</td>
</tr>
<tr>
<td>Infections</td>
<td>28 (24%)</td>
<td>43 (36%)</td>
<td>41 (35%)</td>
<td>28 (27%)</td>
<td>43 (36%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>15 (13%)</td>
<td>23 (20%)</td>
<td>17 (15%)</td>
<td>15 (14%)</td>
<td>23 (20%)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (6%)</td>
<td>11 (10%)</td>
<td>10 (9%)</td>
<td>4 (4%)</td>
<td>9 (8%)</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>3 (3%)</td>
<td>5 (4%)</td>
<td>3 (2%)</td>
<td>2 (2%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>3 (3%)</td>
<td>5 (4%)</td>
<td>3 (2%)</td>
<td>2 (2%)</td>
<td>5 (4%)</td>
</tr>
</tbody>
</table>

*For Studies 1, 3, and 3, events are counted from the beginning of trastuzumab treatment. For Study 4, events are counted from the date of randomization. *Studies 1 and 2 regimens: docetaxel and cyclophosphamide followed by paclitaxel (AC–T) or paclitaxel plus trastuzumab (AC–TH). *Median duration of follow-up for Studies 1 and 2 combined was 8.3 years in the AC–TH arm. *Median follow-up duration of 12 months on the one-year trastuzumab treatment arm. *Study 4 regimen: docetaxel and cyclophosphamide followed by docetaxel (AC–T) or docetaxel plus trastuzumab (AC–TH).

Symptoms were treated with acetaminophen, diphenhydramine, and meperidine (with or without naloxone). The treatment of trastuzumab infusion reactions included discontinuation of trastuzumab infusion for all reactions. Other signs and symptoms such as nausea and vomiting occurred in 21% and 10.5% of patients, respectively. In 14% and 9% of patients, second or subsequent trastuzumab infusions were administered as monotherapy or in combination with chemotherapy, respectively. In the post-marketing setting, severe infusion reactions, including hypotension, anaphylaxis, and angioedema have been reported.

In Arm 2, patients who received trastuzumab and chemotherapy had higher incidence of adverse events compared to those receiving trastuzumab alone. The most common site of infection in the safety population was the respiratory tract (12% vs. 5%), followed by skin and subcutaneous tissue (11% vs. 2%). The incidence of infection was highest in the first 5 months of trastuzumab therapy, and then decreased over time.

In Arm 1, patients receiving trastuzumab and chemotherapy had higher incidence of adverse events compared to those receiving trastuzumab alone. The most common site of infection in the safety population was the respiratory tract (12% vs. 5%), followed by skin and subcutaneous tissue (11% vs. 2%). The incidence of infection was highest in the first 5 months of trastuzumab therapy, and then decreased over time.

The incidence of adverse events varied between the two treatment arms, with Arm 1 having a higher incidence of infections compared to Arm 2. The overall incidence of infections was 12% in Arm 1 and 5% in Arm 2. These differences were statistically significant and were higher in patients receiving trastuzumab and chemotherapy compared to those receiving trastuzumab alone.

Table 6: Per-Patient Incidence of New Onset Myocardial Dysfunction (by LVEF) in Studies 1, 2, 3, and 4

<table>
<thead>
<tr>
<th>LVEF Decrease</th>
<th>LVEF Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF &lt; 10%</td>
<td>LVEF ≥ 10%</td>
</tr>
<tr>
<td>Absolute Decrease</td>
<td>Absolute Increase</td>
</tr>
</tbody>
</table>

*Studies 1, 2, and 3: AC (n = 1856)
see Warnings and Precautions.

Thrombosis/Embolism: In 4 randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher in patients receiving trastuzumab and chemotherapy compared to chemotherapy alone in three studies (2.6% vs. 1.5% [Study 1]; 2.5% and 3.7% vs. 2.2% [Study 4] and 2.1% vs. 0% [Study 9]), and in one [Study 2]. Among women receiving adjuvant therapy for breast cancer, the incidence of NCI-CTC Grade 3 to 5 diabetes (6.7% vs. 5.4% [Study 1]) and of NCI-CTC Grade 3 to 5 diabetes (2.2% vs. 0% [Study 2]), and of Grade 1 to 4 diabetes (7% vs. 1% [Study 1]; one-year trastuzumab treatment at 12.6 months duration of follow-up) were higher in patients receiving trastuzumab as compared to controls. In Study 4, the incidence of Grade 3 to 4 diabetes was higher (5.2% vs. 0.6%) in the trastuzumab-containing arm compared to the chemotherapy only arm. Treatment discontinuation for renal insufficiency/failure was 2.6% on the trastuzumab-containing arm and 0.3% on the chemotherapy only arm.

In the post-marketing setting, rare cases of nephrotic syndrome with nephrotic syndrome on glomerulonephritis were reported. The time to onset ranged from 4 months to approximately 18 months from initiation of trastuzumab therapy. Pathologic findings included mesangial glomerulonephritis, focal glomerulosclerosis, and fibrotic glomerulonephritis. Complications included volume overload and congestive heart failure.

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

Among 1003 women with metastatic breast cancer, human antimurine antibodies to trastuzumab were detected in one patient using an enzyme-linked immunosorbent assay (ELISA). This patient did not experience an allergic reaction. Samples for assessment of HAMA were not collected in studies of adjuvant breast cancer.

Post-Marketing Experience: The following adverse reactions have been identified during post-approval use of trastuzumab. Because these reactions are identified primarily from voluntary reports of adverse reactions that are received by Merck, it is not always possible to reliably estimate their frequency or establish their causal relationship to drug exposure. Infections [see Warnings and Precautions]; Glomerulonephritis or glomerulonephrotic sequence, including pulmonary hypoplasia, skeletal abnormalities, and neonatal death [see Warnings and Precautions]; Embryo-Fetal Toxicity: 

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary:

Trastuzumab products can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of trastuzumab during pregnancy resulted in cases of hydrops fetalis and of hyaluronidase sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death (see Data). Aplasia of the patient’s potential risks to the fetus. There are clinical considerations if a trastuzumab product is used in a pregnant woman or if a patient becomes pregnant within 7 months following the last dose of a trastuzumab product (see Clinical Considerations). The estimated risk of major birth defects and miscarriage for the indicated population is unknown. 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.

Clinical Considerations:

Fetal/Neonatal Adverse Reactions — Monitor women who received Ogivri during pregnancy or within 7 months prior to conception for hydrops fetalis. If hyaluronidase occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data — In post-marketing reports, use of trastuzumab during pregnancy resulted in cases of hyaluronidase and of hyaluronidase sequence, manifesting in the fetus as pulmonary hypoplasia, skeletal abnormalities and neonatal death. These case reports described hyaluronidase in pregnant women who received trastuzumab either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after trastuzumab was stopped. In one case, trastuzumab therapy resumed after amniotic index improved, and hyaluronidase reoccurred.

Animal Data — In studies where trastuzumab was administered to pregnant cynomolgus monkeys during the period of organogenesis at doses up to 25 mg/kg given twice weekly (up to 25 times the recommended weekly human dose of 2 mg/kg), trastuzumab crossed the placental barrier during the early (gestation Days 30 to 50) and late (gestation Days 120 to 150) phases of gestation. The resulting concentrations of trastuzumab in fetal serum and amniotic fluid were approximately 33% and 25%, respectively, of those present in the maternal serum but were not associated with adverse developmental effects.

Lactation

Risk Summary:

There is no information regarding the presence of trastuzumab products in human milk, the effects on the breastfed infant, or the effects on milk production. Published data support human IgG is present in human milk but does not enter the neonatal and infant circulation in substantial amounts. Trastuzumab was present in the milk of lactating cynomolgus monkeys but not associated with neonatal toxicity (see Data). Consider the developmental and health benefits of breastfeeding along with the mother’s clinical need for Ogivri treatment and any potential adverse effects on the breastfed child from Ogivri or from the underlying maternal condition. This consideration should also take into account the trastuzumab product washout period of 7 months (see Clinical Pharmacology).

Data:

In lactating cynomolgus monkeys, trastuzumab was present in breast milk at about 0.3% of maternal serum concentrations after pre-Neonatal (gestation Day 120) and post-Neonatal (through post-neonatal Day 24) doses of 25 mg/kg administered twice weekly (25 times the recommended weekly human dose of 2 mg/kg of trastuzumab products). Infant monkeys with detectable serum levels of trastuzumab did not exhibit any adverse effects on growth or development from birth to 1 month of age.

Females and Males of Reproductive Potential

Pregnancy Testing:

Verify the pregnancy status of females of reproductive potential prior to the initiation of Ogivri.

Contraception:

Females — Trastuzumab products can cause embryo-fetal harm when administered during pregnancy. Advise females of reproductive potential to use effective contraception during treatment with Ogivri and for 7 months following the last dose of Ogivri [see Use in Specific Populations and Clinical Pharmacology].
MBC Treatment Is Unaligned With NCCN Guidelines Leads to Higher Patient Cost Responsibility

WHAT IS THE IMPACT on the patient responsibility portion of cancer treatment that differs from care guidelines?

In the case of metastatic breast cancer (MBC), it is already known that treatment that is not in concordance with the National Comprehensive Cancer Network (NCCN) is linked to higher healthcare usage and patient costs. A study published in the October issue of JNCCN—Journal of the National Comprehensive Cancer Network extends those findings, saying that that patients with MBC who are on Medicare and receive treatment that is discordant with NCCN guidelines bear a greater burden of cost responsibility than patients who do receive care according to the guidelines.

The previous work found that about one-fifth of Medicare beneficiaries with MBC have received treatment that did not align with NCCN guidelines. Although no overall survival difference was seen between patients with and without guideline-concordant care, those without had almost $2000 higher Medicare spending per month.

The additional data come as those who work in oncology, from providers to social workers, are increasingly discussing the issue of financial toxicity with their patients, because new treatments are getting more expensive, the authors noted. Financial toxicity is linked to negative patient outcomes and psychological stress, and adults over age 65 may be particularly sensitive to this issue, given the likelihood that they live on a fixed income.

In an interview with The American Journal of Managed Care®, lead author Courtney P. Williams, MPH, in the Division of Hematology and Oncology at O’Neal Comprehensive Cancer Center at the University of Alabama, Birmingham, said that this is the first study to look specifically at patient cost responsibility and was conducted to fill in gaps unanswered by the earlier study.

SEER-Medicare data, which the retrospective study used, do not provide true out-of-pocket costs, Williams said, but do show co-payments, coinsurance, and deductibles. However, that information alone does not reveal if those costs were paid by the patients or picked up by a supplemental Medicare plan or charity.

The researchers examined patient costs for 3709 women who received MBC diagnoses between 2007 and 2013 and survived at least a year after diagnosis. Treatment regimens were matched to the version of the NCCN breast cancer guidelines that were available at the time of treatment. Out of the 3709, 17.6%, or 651, received guideline-discordant treatment.

Compared with patients receiving guideline-concordant care, those receiving discordant treatment were younger and more often Medicare/Medicaid dual eligible, hormone receptor (HR) negative, and human epidermal growth factor receptor 2 (HER2) positive.

Researchers reviewed treatment regimens for guideline discordance and grouped them into categories including:

- Therapy mismatched with HR or HER2 status
- HER2-targeted therapy without chemotherapy
- Nonapproved bevacizumab use
- Adjuvant regimens received in the metastatic setting
- Miscellaneous reasons for guideline discordance, including nonapproved agents or regimens usually received in cancers other than MBC, trastuzumab in nonapproved combinations, and approved agents or regimens received in nonapproved year

In the year after diagnosis, median patient cost responsibility was significantly higher for discordant versus concordant care: $7421 (interquartile range [IQR], $4359-$12,983) vs $5171 (IQR, $3006-$8483); P < .001.

In adjusted models, guideline-discordant treatment was significantly associated with $1841 higher patient costs in the first year from diagnosis (95% CI, $1260-$2401) compared with guideline-concordant care.

Treatment regimens were matched to the version of the NCCN breast cancer guidelines by Allison Inserro, Maggie L. Shaw, and Laura Joszt

Patient cost responsibility differed by category of discordance, with those receiving nonapproved bevacizumab having the highest cost responsibility (β = $3330; 95% CI, $1711-$4948).

“I think that guidelines exist for a reason, and even though out-of-pocket costs are not considered when creating the guidelines, these are evidence-based physician-recommended treatments that ideally have better outcomes for patients, and that’s why they are included as guideline-based therapy,” Williams said. Although she noted that there may be situations in which off-guideline treatment is appropriate, she said she thinks the study adds to the knowledge that, in addition to leading to better outcomes for patients, using guidelines-based treatment increases the likelihood of reduced financial toxicity.

The problem of financial toxicity is not expected to go away in Medicare beneficiaries, according to Williams.

“I think that looking at cost to patients in this population is important,” she said. “In this population, financial toxicity will continue to be a growing problem because these patients are increasing in survival based on these new treatments, and also, these new treatments are becoming more and more expensive.”

REFERENCE


Medicare Patients With Blood Cancer Face High Costs That May Affect Treatment

ALTHOUGH SURVIVAL RATES for older patients with blood cancers have improved with the introduction of more efficacious and less toxic therapies, rising healthcare costs mean that less than half of patients are receiving treatment for their cancer shortly after their initial diagnosis, according to an October 2019 Milliman report commissioned by the Leukemia & Lymphoma Society (LLS).1

The study included an analysis of costs incurred by Medicare beneficiaries with newly diagnosed acute leukemia, chronic leukemia, lymphoma, multiple myeloma, or bone marrow disorders. The investigators identified 35,877 fee-for-service (FFS) beneficiaries and 1898 beneficiaries with Medicare Advantage with Part D coverage (MAPD) in 2015 using the Medicare research identifiable Part A, B, and D FFS database and Milliman’s proprietary MAPD database.

"Along with the substantial healthcare costs associated with treatment of patients with blood cancer comes substantial OOP [out-of-pocket] costs for patients,” the authors wrote in the report. “In particular, because of the Medicare Part A, B, and D benefit design, the OOP burden can be greater for Medicare beneficiaries compared to commercially insured patients.”

Among the patients with newly diagnosed blood cancer, just 43.7% of MAPD beneficiaries and 38.7% in FFS received an anticancer therapy within 90 days of getting their diagnosis. Patients with lymphoma were most likely to receive therapy (24.7% for MAPD and 21.4% for FFS), and patients with bone marrow disorder were the least likely (2.5% for MAPD and 2.3% for FFS).

In the month of diagnosis, which is the most expensive for all patients with blood cancer, the average spending per FFS beneficiary was $17,719, with acute leukemia costing the most ($35,202) and chronic leukemia, the least ($11,568). The average spending per MAPD patient was $14,691. Acute leukemia still cost the most ($35,202), but bone marrow disorder cost the least ($8,848). However, by the end of 2 years, multiple myeloma brought the most costs for MAPD patients ($178,496), with acute leukemia a close second ($177,543).

OOP spending also varied by cancer type, ranging from $588 (chronic leukemia) to $1201 (lymphoma) for MAPD patients in the month of diagnosis and from $1268 (chronic leukemia) to $2144 (multiple myeloma) for FFS patients.
“With the substantial allowed costs incurred by patients newly diagnosed with blood cancer, patients who do not qualify for government subsidies can accumulate significant OOP spending,” according to the authors.

By the end of year 2, the greatest difference in average OOP spending per patient was between MAPF and FFS beneficiaries who had acute leukemia ($7644 vs $21,852), with the smallest difference for patients with chronic leukemia ($4379 vs $11,224).

“In addition to the emotional impact of dealing with a blood cancer, patients and families often face extraordinary costs in the first year after diagnosis and beyond,” Louis J. DeGennaro, PhD, LLS president and chief executive officer, said in a statement. “The Leukemia & Lymphoma Society hopes that the findings from this new study will prompt payers, providers, patient advocates, and policy makers to work together to address the financial burdens for patients.”

In 2018, LLS commissioned a separate study from Milliman on the difference between costs for patients with blood cancer versus other cancers. That study used commercial claims and found that patients with blood cancers are burdened with higher costs than those with other cancers and that those costs persist over time and never drop to precancer levels.1

REFERENCES

ASCO Updates Patient-Centered Oncology Payment Model

IN 2014, THE AMERICAN SOCIETY OF CLINICAL OF ONCOLOGY (ASCO) released its first alternative payment model, Consolidated Payments for Oncology Care, aimed at reducing overall spending on cancer care (eg, by preventing unnecessary hospitalizations) and increasing revenue for oncologists. That original model also promised 10% raises to practices that scored high on quality-care measures, while those that fell short could be docked the same amount. ASCO promised limited financial risk under this model.2

That was followed in 2015 by the then-proposed Patient-Centered Oncology Payment (PCOP) model that promised a more flexible payment model to help oncology practices deliver the right care at the right price while holding the practices accountable for actually delivering that care.2

Now, after a request for additional input from oncologists, practice administrators, payer representatives, and experts in physician payment and business analysis, ASCO has issued updated guidance on PCOP With CMS’ Oncology Care Model set to end in 2021, the current draft of ASCO’s Community-based Oncology Medical Home model would be an option to take its place, building on feedback from pilot programs and concerns that the first PCOP model was not specific enough.1 CMS has also proposed Oncology Care First to debut in 2021 (See Cover story).

This new ASCO model “has requirements that practices have to follow in the way they deliver care, and this satisfies the concerns of payers,” said Jeffery Ward, MD, past chair of ASCO’s Government Relations Committee and a contributor to PCOP The update also has made clinical pathways a cornerstone of care delivery. ASCO hopes to deliver on the promises of PCOP using 3 approaches: (1) improving the delivery and coordination of care, (2) developing a performance-based reimbursement system, and (3) consistently delivering high-quality care.

“We’re stewards of our patients’ well-being, and ASCO’s model reflects everything we have learned in over 50 years of work to advance patient care,” ASCO President Howard A. “Skip” Burris III, MD, FACP, FASCO, stated. ASCO projects PCOP could save up to 8% across the healthcare system. ●

REFERENCES

Treatment Facility and Provider’s Patient Volume and Sharing Influence Survival in Patients With MM

THE FINDINGS OF A STUDY published in the journal of the National Comprehensive Cancer Network (NCCN) revealed that where patients with multiple myeloma (MM) get treatment and whether the facility treats many patients with MM can affect survival.

The population-based study investigated a previously identified group of patients that share at least one characteristic. Disease risk, drug response, survival, or even cancer type can serve as a survey’s backbone.

After identifying patients with common characteristics and using claims-based data, researchers from BC Cancer in Victoria, British Columbia, Canada, and the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center and UNC Gillings School of Public Health in Chapel Hill recently investigated 2 theories among patients with MM:1

1. Patients evaluated at an National Cancer Institute–designated Comprehensive Cancer Center (NCICCC) have a longer overall survival (OS) compared with those assessed elsewhere.
2. Treatment by high- or low-volume providers who share patients with an MM specialist improves survival.

For their study, the authors wanted to expand on previous results suggesting that outcomes are improved among patients with MM treated at high-volume facilities compared with other facilities. They said they wanted to learn more about “the relative contribution of provider expertise and hospital resources to improved outcomes,” which were unknown at the time.1

Leaders of community oncology clinics have resisted the argument that treatment at academic medical centers results in better outcomes, saying that many community practices offer access to clinical trials at a lower cost with less travel burden on patients.

Patients were identified using the UNC Cancer Information & Population Health Resource (CIPHR). They had to be aged 18 or older and have received their MM diagnosis between 2006 (when Medicare Part D became available) and 2012 (most recent complete year of data available when the study was done). The extensive patient exclusion criteria included additional cancer diagnoses, incomplete CIPHR data on home or provider zip code, lack of continuous insurance coverage for the 6 months before and 12 months after diagnosis, chemotherapy not received in the 12 months following diagnosis, and simultaneous coverage with Medicare, Medicaid, and private insurance. The result: a study population of 1029 patients, with a mean age of 68 years. Treatment facility, provider volume, and patient sharing between MM specialists and community providers were investigated for their effects on patient survival. »
For treating facility, a patient had to have at least 1 outpatient visit with an NCICCC oncologist in the year after diagnosis, and provider volume was defined as number of patients with MM per provider in the 2 years before diagnosis. Patient sharing was 2-fold:

1. NCICCC oncologists: Two had to have at least 1 patient with MM in common in the 2 years before diagnosis.

2. Community oncologists: They had to share at least 10% of their patients with an NCICCC MM specialist.

Covariates were age, sex, race, marital status, insurance type, distance between home and NCICCC clinic, hospital referral region, activities of daily living dependency score, rural versus urban zip code, and sociodemographics (quartiles of median household income, percentage of population unemployed, percentage of population with college degree).

NCICCC MM specialists who were the primary treating physicians for patients with MM and evaluation at an NCICCC meant lower mortality risk for patients. There was a 22% higher risk of death after treatment at the lowest-quartile facilities (less than 4 new patients with MM per year) compared with the highest quartile (at least 10 new patients per year). Mortality risk was higher among patients treated by community oncologists; high- and low-volume status and patient-sharing history made no difference. Mortality rates were equal, however, between patients who received treatment from NCICCC MM specialists and the highest-volume community oncologists.

The study authors said these results add to an already strong body of data that “patients with MM benefit from care at high-volume facilities, and suggest that similar outcomes can be achieved by the highest-volume providers in the community.” To improve outcomes among these community providers, the authors suggested earlier adoption of new drugs, earlier recognition of problems and progressive disease, and quick access to nononcology specialties such as orthopedics and nephrology. They also believe that any patient sharing with an MM specialist is beneficial because of the rarity of MM.

Possible study limitations included lack of coverage of other survival factors, such as disease stage, cytogenetics, and clinical trial involvement; a likely incomplete definition of “patient sharing”; treatment regimens incorrectly noted or misclassified due to varying degrees of claim specificity; and inability to gauge provider patient volume correctly.

References

Novel Drugs for MM Take Longer to Reach Black, Hispanic Patients Than White Patients

African American and Hispanic patients with multiple myeloma (MM) are not receiving state-of-the-art therapies as quickly as white patients, according to a study published October 17, 2019, in the journal Blood Advances.1

Moreover, the differences cannot be attributed to insurance coverage, because the investigators conducted the study using the SEER-Medicare database. The findings showed that, on average, it took nearly 2 months or longer for patients of color to receive immunomodulatory drugs such as lenalidomide and/or proteasome inhibitors such as bortezomib and carfilzomib. The use of these therapies more than doubled survival of patients with MM within the past decade.

The investigators also found that Hispanic patients had the highest medical costs: $12,657 versus $11,546 for African Americans and $10,143 for whites. The authors said the higher costs could stem from greater hospitalization costs, possibly because of complications due to treatment delays. However, the delays did not seem to affect overall survival, which was similar overall (2.6-2.8 years).

MM is relatively rare but more common in African Americans compared with whites and more common in men than women.

“We noted that minorities are not getting introduced to treatment early enough to derive adequate clinical gains,” said lead author Sikander Aliawadhi, MD, of Mayo Clinic’s campus in Jacksonville, Florida, in a statement. “Since our analysis is based on Medicare patient data, these disparities cannot be attributed to differences in insurance coverage. Patients are not receiving treatment equally even in this ostensibly equal-access setting.”

Researchers reviewed data from the SEER-Medicare database from 2007 to 2013. The study included 3504 white patients, 858 African Americans, and 468 Hispanics. The average length of time between MM diagnosis and start of treatment for white patients was 2.7 months compared with 4.6 months for Hispanics and 5.2 months for African Americans.

All groups had an increasing trend of starting therapy within 6 months of MM diagnosis, particularly whites (all P < .05). MM-specific survival (MSS) was significantly longer for African Americans (5.4 years) than whites (4.5 years; P < .05) and comparable for Hispanics and whites.

MM treatment guidelines, including those from the National Comprehensive Cancer Network and the Mayo Stratification for Myeloma and Risk-Adapted Therapy, recommend bortezomib- and/or lenalidomide-based regimens as first-line therapy for newly diagnosed MM, with pomalidomide- and carfilzomib-based regimens recommended for relapsed/refractory MM. In addition, autologous stem cell transplant (ASCT) remains the standard of care for transplant-eligible patients, providing a larger benefit the earlier it is used.

Rates of ASCT within 1 year of diagnosis rose among whites and African Americans but not for Hispanics, who were less likely to receive ASCT versus whites.

The investigators conducted this study to address knowledge gaps that exist with the introduction of these newer drugs. Findings from related previous studies, for example, noted a rising trend in ASCT use for all groups except African Americans. The extent of racial disparities in use of the newer therapies was not known.

The study had several limitations, such as the fact that the database did not include a clinical measure of disease severity; MM has several subtypes that may introduce unmeasured bias, the authors said. For instance, African Americans may have less severe forms of MM, which may explain why despite unequal access to new drugs, their MSS is significantly longer than that of whites.

“Addressing these disparities could lead to more equitable healthcare utilization and clinical benefit for all patients with MM, regardless of race/ethnicity, and address the trend of increasing differences in treatment access, healthcare costs, and outcomes between these groups,” concluded the authors.

References

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Carolyn Starrett, Senior Vice President of Provider Solutions, Flatiron Health

What are some features Flatiron recently added or will soon add to help streamline practice operations?

It’s one of our big investment themes for the year. One of the biggest projects we’ve embarked on is a new framework that exists within our EHR [electronic health record] and our group in-boxes. That effectively enables practices to create a group of team members who are responsible for tackling any given problem in the EHR.

We started around preauthorization for drugs and around centralized scheduling, and this allows teams to work together in a collaborative environment where they can all see the status and progress of what’s happening and then manage against a work list of all the different tasks that have to happen to get those things done. It’s a whole new framework for us, so we’re super-excited about all the different applications we might have on top of that and are just starting to explore new use cases—things around, for example, financial counseling.

How do you take any 17-step process that needs to happen in a practice to drive toward an outcome—of which, unfortunately, there are many, many—and organize that so you can get the right people to see the right information at the right time and then work collectively to run that process as efficiently as possible? I think that’s one of the biggest investments we’ve made in the last year. •

Erich Mounce, Chief Operating Officer, OneOncology

If a practice isn’t doing well on cost savings or achieving high-quality care, how does OneOncology approach adjusting provider practices?

Well, I think the beauty of OneOncology is [that] it’s not this cookbook process. It’s not “Here’s our only way to do it, and if you don’t do it this way, we come hit you with a club.” I think it’s a variation of themes. We’ve got some practices [that] really restrict regimens. We have some practices that have a little bit more selection of preferred regimens. It’s an education process and a rapid learning cycle of how those data are recirculated back. So, the first thing we do is measure where they are and then start to feed back data. Then we also show them [what would happen] if they would [comply] a little bit more [with] this pathway or perform a little bit better under this contract: “Look how that will affect either your compensation or profitability.” So, it’s really taking all of that data and constantly feeding back accurately and allowing the doctors to buy into that. That really does tend to move physician behavior a lot more than just saying, “You guys aren’t doing well—you need to do it this way.” •

Lee Schwartzberg, MD, FACP, Executive Director, West Cancer Center; Chief Medical Officer, OneOncology

OneOncology announced that its practices have begun administering the 2 cancer biosimilars on the US market. How will this help address financial toxicity?

We were very proud that OneOncology jumped in as the first group to endorse therapeutic biosimilars in the oncology space. We really believe that biosimilars line up as a value accretion for every constituency, whether it’s the patient, the practice, or the payer, because you’re giving a high-value drug at a lower cost and therefore, across the chain of value, it’s good for everyone. So, there’s education around biosimilars. We’ve been using supportive care biosimilars for a few years. Some people feel there might be a different bar for therapeutics. I’ve looked at the totality of evidence about what allows a biosimilar to come to market, which is based on a very strong analytic similarity, as well as some clinical trials. We can extrapolate the use of these drugs into the same conditions that we would with the originator drug, I feel very strongly that we’re going to move wholesale into using biosimilars where they’re appropriate in the therapeutic oncology space, and it will be great for everyone.

“Patients have been very comfortable making a therapeutic switch when their doctor explains to them that they’re getting a drug that’s just like the other drug. It’s not a generic; it’s analogous to a generic. Biosimilars are for biologics, and they’re slightly different.”

—Lee Schwartzberg, MD, FACP, Executive Director, West Cancer Center; Chief Medical Officer, OneOncology

How important is it to collaborate with physicians to make sure they are comfortable prescribing biosimilars and to alleviate any concerns they may have?

There’s still an educational gap about biosimilars. It’s still a very new product in the oncology market. We have to understand that biologics are inherently complicated to make, so we have to be comfortable that they are being made the same way regardless of who is manufacturing them. We are comfortable with the current therapeutics that are out there.

There will be more [biosimilars] coming. How exactly we [administer them] operationally is a challenge, whether we’re changing patients [to a new drug] or new starts, each of these drugs is a different drug so we have to have a care
plan or a regimen plan that includes those. So, there’s some operational charac-
teristics that have to be worked out, and we’re working through those at OneOncology practices.

For the physicians, there’s still an educational component, and the same is true for the patients. Although really, patients have been very comfortable with making a therapeutic switch when their doctor explains to them that they’re getting a drug that’s just like the other drug. It’s not a generic, but it’s analogous to a generic. Generics are only for small molecules. Biosimilars are for biologics, and they’re slightly different.

Lawrence N. Shulman, MD, Director, Center for Global Cancer Medicine, Abramson Cancer Center; Professor of Medicine, Hospital of the University of Pennsylvania

In what ways can value-based care advance the quality of oncology care that it isn’t currently doing?

I think that value-based care can start to make us concentrate on what’s best for the patients but what’s also reasonable. In the United States, we sometimes have this mind-set that more is better—and sometimes in medi-
cine, more is not better. We have to make the best decisions. In value-based care or any other payment model, we still want to give our patients the best chance to do well. But we also need to take out of care what is not beneficial and in fact sometimes is harmful to patients.

We know there has probably been more chemotherapy given in the last 2 weeks of life than we should do that doesn’t really benefit patients and, in fact, may hurt them. We know that we don’t use hospice care at the end of life as much as we probably should. We know we probably do too many scans that really don’t change the way that we approach the patient and don’t improve their survival or overall quality of life. I think we just need to be more careful about that. Value-based care makes us think a little more about it and shares responsibility, if you will, with us and how we make those decisions.

Bobby Green, MD, Chief Medical Officer, Flatiron Health

Is Flatiron working to better analyze and recognize when a patient’s condition is getting worse based on real-world data included in the electronic health record (EHR)?

One of the problems we have—and I think this gets back to the power of real-world data—is [that] right now, when we treat a patient with cancer, for most of our therapies, the cancer treatment works in some percentage of patients and it doesn’t work in another percentage of patients. Most of the time we don’t know how to identify [which] patients are going to respond to therapy and [which ones] will not respond to therapy. At the same time, during their routine care, we’re collecting an enormous number of factors...maybe genomic data, maybe their genomic profiles, [to gain an understanding of] what those genomic profiles of the tumors are, and then with real-world data we can understand, when do patients respond and when do patients not respond? So, we are pooling together that data, whether [they’re] your typical retrospective data or whether [it involves] prospective data, and thinking about: How do we collect genomic data or other information prospectively? Once you have that and you can put it together, you can start to say, “What are the patterns that we see in patients who respond, what are the patterns we see in patients who don’t respond?” and then use that information, ultimately, to help clinicians at the point of care understand who they should be treating with certain agents.

In your work with Flatiron and community oncologists, in what ways have you seen how community oncology is using these tools to essentially be at the forefront of innovation for giving quality care to patients?

One of the amazing things about community oncology practices is that they serve a bunch of different functions or a bunch of different needs. First of all, they’re in the communities where most people live, so they give patients this convenience that you can’t always get. I think, most importantly, what’s really exciting about most community oncology practices is [that] whether they’re small practices or large practices, they all tend to have an entrepreneurial spirit, and that translates into really innovating and coming up with new and interesting ideas on how to deliver better care for patients, and we see that in a variety of areas. I think the most notable is [that] when we think about value-based care and alternative payment models, community oncology has really led the space, both from the standpoint of thought leadership and how we’ve...developed a lot of these plans but also in participation and influence at the highest levels of government. So, if you think about the Oncology Care Model, which is Medicare’s value-based care program, the major driving influences in that in a lot of ways [involve] a variety of community oncology practices—big practices and small practices. So, I think ultimately, it’s that entrepreneurial spirit within community oncology practices and their flexibility that have allowed them to really innovate in a variety of areas in the space.

Michael Kolodziej, MD, FACP, Chief Innovation Officer, ADVI Health

With more value-based agreements being introduced, do you think payers will become more comfortable with paying for one-time, curative treatments with high price tags?

Oh that’s much harder. I think the question of how we’re going to pay for, let’s start with CAR T-cell or gene therapy or what-
ever else the next thing is. I think we are not even close to a solution for that. In fact, we know, for example, that Medicare has completely fumbled the ball. They have not done very well with how they pay for CAR T. Now, mind you, CAR T is mostly inpatient right now. But the [diagnostic-related group is] messed up, the outlier payments require that providing facility to literally lie about how much they spend on the drug. So, it’s all messed up.

Commercial payers right now—because they’re relatively rare events—are just doing what commercial payers do. They negotiate on the individual patient level, and as we’ve seen literally [in recent weeks], Cigna and CVS/Aetna have come out with, let’s just call them old-school models for dealing with risk. Nothing very exciting. So, I’m hoping that as we get more therapies in this space, we’ll see some evolution in the thinking to a more innovative approach. For example, I love the idea of an outcomes-based contract. We haven’t really seen very many outcomes-based contracts in this space. ... I think the idea that we’re going to pay for value, the value that they bring: this should resonate with all payers.

Now, there’s a very important proviso, and that is that these are, in fact, curative therapies, and if anybody thinks they know they are curative ther-

experiences, they’re nuts. The follow-up just has not been long enough and there haven’t been enough patients treated. So, let’s hope that the science does in fact bear out and we do enjoy the kind of benefits that these therapies might provide us.
Empower Physicians to Fight Financial Toxicity With Biosimilars

Kathy Oubre, MS

Biosimilars offer lower-cost alternatives to the biologic agents driving up the cost of prescription drugs. Biologics accounted for nearly 75% of the annual increase in net US spending on medicines in 2018. The availability of biosimilars introduces competition based on price, offering a lower-cost alternative in the short term and helping to restrict—or even reverse—longer-term price growth. As a growing number of biologics used in oncology treatment, such as trastuzumab, encounter biosimilarity competition, providers have the opportunity to significantly reduce prescription drug costs for their patients. Where biosimilars, which are certified as clinically equivalent by the FDA, are the correct treatment option, failure to prescribe them is a failure to address financial toxicity. Ultimately, it’s a failure to hold the oncology profession to the highest, most comprehensive standard of patient care.

Although provider education can play an important role in biosimilar uptake, in certain cases, patients’ insurers prevent providers from prescribing these products. Anticompetitive rebating practices ("rebate walls") by originator manufacturers incentivize payers to adopt “fail-first” preferences for costlier originator drugs, eliminating a patient’s option to choose a lower-cost biosimilar when available. Because biosimilars are clinically equivalent, a fail-first policy preferring an originator is an effective ban on coverage of its biosimilars.

In a higher-profile case of rebate-induced limiting of patient and prescriber choice, UnitedHealthcare adopted a fail-first preference for Amgen originator biologic Neulasta over pegfilgrastim biosimilars Udenyca and Fulphila. This summer, the Federal Trade Commission initiated an investigation of Johnson & Johnson’s contracting practices surrounding infliximab originator Remicade, examining potential exclusionary conduct against surrounding infliximab originator Remicade, of Johnson & Johnson’s contracting practices to restrict—or even reverse—longer-term price growth. As a growing number of biologics used in oncology treatment, such as trastuzumab, encounter biosimilarity competition, providers have the opportunity to significantly reduce prescription drug costs for their patients. Where biosimilars, which are certified as clinically equivalent by the FDA, are the correct treatment option, failure to prescribe them is a failure to address financial toxicity. Ultimately, it’s a failure to hold the oncology profession to the highest, most comprehensive standard of patient care.

CONTINUED FROM COVER

Financial Toxicity With Biosimilars

UnitedHealthcare Patients Will Switch to Biosimilar Epoetin Alfa in 2020

Coverage by Kelly Davio

UNITEDHEALTHCARE HAS REVISED its community and commercial plans’ coverage of erythropoiesis-stimulating agents, according to a November 1, 2019, plan revision. Effective January 1, 2020, patients who are receiving the reference epoetin alfa, Epogen or Procrit, will be required to switch to Pfizer’s biosimilar, Retacrit.

Patients who wish to remain on the reference epoetin alfa will need to meet medical necessity criteria; Epogen or Procrit is considered medically necessary if a patient had minimal clinical response to Retacrit and a physician attests that a superior response would be expected from Epogen or Procrit, or if the patient has a history of intolerance to, contraindication to, or failure of Retacrit that a physician attests would not be expected with Epogen or Procrit.

Additionally, coverage for Retacrit will not require prior authorization for patients who meet diagnosis-specific criteria for indications including anemia due to chronic kidney disease, anemia due to chemotherapy, and anemia associated with myelodysplastic disease.

The new policy does not apply to community plans in Kansas or Louisiana.

This revision to UnitedHealthcare’s coverage comes after the payer made a prior notable move to prefer biosimilars of anti-cancer drugs. In August of this year, UnitedHealthcare indicated that starting in October, it would prefer Amgen’s biosimilar bevacizumab (Mvasi) and biosimilar trastuzumab (Kanjinti), to the reference drugs, Avastin and Herceptin, respectively.

UnitedHealthcare has also made biosimilar filgrastim (Zarxio) a preferred product over follow-on filgrastim (Granix, or tbo-filgrastim), the reference filgrastim (Neupogen), and a competing biosimilar, filgrastim (Nivestym).

Finally, a representative from UnitedHealthcare previously told The Center for Biosimilars® in an email that the payer planned to add biosimilar infliximab (Inflectra) to a preferred position along with the brand-name infliximab (Remicade).

REFERENCES

Payers can argue that the savings from larger rebate packages accrue to the benefit of their entire insured population. However, any savings that from contracts that exclude oncology biosimilars come at the direct expense of the patients who are forced to pay higher out-of-pocket costs for expensive originator biologics.

Today, however, payers have the option to simply do the right thing, rejecting attempts to block biosimilar access and respecting physicians’ ability to prescribe as they know best. If only they’re allowed to compete on a level playing field, biosimilars may hold the key to savings for patients struggling with financial toxicity. The oncology provider community should demand better, making clear that antibiosimilar formulary policies infringe on providers’ ability to offer care in a manner that promotes the best outcomes for our patients.

AUTHOR INFORMATION
Kathy Oubre, MS, is the chief operating officer of Pontchartrain Cancer Center, with locations in Covington and Hammond, Louisiana.

REFERENCES

First Rituximab Biosimilar, Truxima, Launches in United States

TEVA AND CELLTRION LAUNCHED their biosimilar rituximab, Truxima, in the United States, with the product reaching patients beginning November 11, 2019. Truxima is being offered at a 10% discount off the list price of reference product Rituxin.

“Truxima will be available for $845.55 for a 100-mg vial and $4227.75 for a 500-mg vial, though these costs do not take into account additional rebates or discounts that may apply. We are pleased to announce the launch of the first rituximab biosimilar, Truxima, with our marketing partner Teva in the United States,” Hyoung-Ki Kim, vice chairman of Celltrion Healthcare, said in a statement. “We believe that the introduction of Truxima into the United States market will contribute to addressing unmet needs of United States patients as well.” Teva is also offering patient support services through its Comprehensive Oncology Reimbursement Expertise program.

Truxima was approved by the FDA in November 2018 to treat adults with CD20-positive, B-cell non-Hodgkin lymphoma either as monotherapy or in combination with chemotherapy. Like its reference product, Truxima has a label that carries a boxed warning alerting providers and patients to the risk of fatal infusion reactions, skin and mouth reactions, hepatitis B reactivation, and a rare but serious brain infection. The drug is also approved to treat chronic lymphocytic leukemia.

Notably, although the reference rituximab also carries indications for inflammatory diseases including rheumatoid arthritis, Celtrion sought approval only for indications in oncology; when members of the FDA’s Oncologic Drugs Advisory Committee asked about the reasoning behind seeking indications in cancer treatment only, a Celtrion representative stated, “We are only seeking approval in 3 [oncology] indications given the patent and exclusivity landscape at this time.”

In light of a patent settlement with Genentech, however, Celtrion and Teva are now submitting an application to the FDA for the indications of rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis.

News of the launch comes shortly after Pfizer, the license holder of the other FDA-approved rituximab biosimilar, Ruxience, announced its plans to launch its product in the United States in January 2020.

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Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical therapies to improve standards of care and address diversified, unmet medical needs of people globally by leveraging our world-class science and technology.

With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 15,000 employees around the world draw upon a rich legacy of innovation and a robust pipeline of promising new medicines to help people. In addition to a strong portfolio of medicines for cardiovascular diseases, under the Group’s 2025 Vision to become a “Global Pharma Innovator with Competitive Advantage in Oncology,” Daiichi Sankyo is primarily focused on providing novel therapies in oncology, as well as other research areas centered around rare diseases and immune disorders.

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CONTINUED FROM COVER

OCF is built on the same framework as other recently announced Medicare “First” models, including Primary Care First and Kidney Care First. These models offer prospective payments for providing enhanced care services to an aligned patient population and hold providers accountable for quality and cost through retrospective performance-based payments (PBPs). The OCF RFI retains many of the favorable facets of the OCM program, including its voluntary status, the opportunity for oncologists to earn additional revenue by reducing expenditures for 6-month episodes of care for Medicare beneficiaries undergoing chemotherapy, and its qualification as an advanced alternative payment model (APM) under the Quality Payment Program, created by the 2015 Medicare Access and CHIP Reauthorization Act (MACRA).6

The second-generation oncology bundled payment model also strives to improve key aspects of the original program that unintentionally created disincentives for providers. One notable change is a potential revision to how CMS adjusts for new, high-cost drugs. In OCM, one of the only Medicare risk models holding participants accountable for Part D drug expenditures, the novel therapies adjustment is applied at the participant level across all cancer types in aggregate. Because novel therapies are not consistently or uniformly available among different cancer types, the single novel therapy adjustment has created advantages and disadvantages for OCM participants at the practice level because of variation in the mix of cancer types among peer practices and within a singular practice over time. CMS’ consideration in OCF to apply the novel therapy adjustment separately for each cancer type would improve this misalignment. Similarly, a trend factor applied separately by cancer type would remove unfair rewards or penalties that result from variation in patient mix, both internally over time and compared with other groups.

Archway Health’s analysis of 28 OCM practices suggests that to successfully use cancer-specific trend factors and novel therapies adjustments, covariates in the model need to be better calibrated. For example, attributes such as radiation therapy or lung cancer are too strongly correlated with PBPs instead of price, pointing to a flaw in the OCM model. We expect that running a separate regression for each cancer type, similar to how CMS runs a separate regression for each episode of care in the Bundled Payment for Care Improvement (BPCI) Advanced program, will better calibrate covariates.

In OCF, CMS also proposes to improve the alignment methodology for the prospective monthly management payments. In OCM, Monthly Enhanced Oncology Services payments are not available for patients receiving only hormonal therapy when no evaluation and management visit occurs within the 6-month episode period, which led to attribution-related frustration among participants early in the model. In OCF, aligned beneficiaries covered in the Monthly Population Payments (MPPs) include patients undergoing hormonal therapy only, as well as those under active surveillance or survivors of cancer undergoing care management from their oncologist.

CMS is also changing its approach to getting providers to take risk in OCF. The potential model would have 3 risk tracks that allow providers to pick their pace of assuming risk. Two of these tracks would force downside risk onto current OCM participants immediately, and the third would allow new providers to stay in an upside-only arrangement for 2 performance periods. This contrasts with OCM, in which participants originally could stay in the upside-only arrangement indefinitely. After the program launched, CMS amended the program and required practices to earn a PBP to stay in the upside-only track. In December 2019, OCM practices that have yet to earn a PBP will be required to switch to the 2-sided risk track or be forced to drop from the program. The OCF RFI indicates that CMS is pushing providers toward assuming downside risk and also recognizing that some organizations need to get their bearings first in a new program before being held accountable.

Although the OCF RFI incorporates learnings from OCM, it does not seem to take into account the social determinants of health (SDOH), a critical consideration for any care management model and today’s healthcare environment. Social determinants, including access to transportation and healthcare services, affect a wide range of health outcomes and risks. As an example, oncologists treating patients who live in rural areas may face greater barriers to having patients attend visits and appointments than providers treating patients in areas with more transportation options and less burdensome commutes. Greater consideration for SDOH should be a goal of the OCF RFI process.

The OCF RFI comes on the heels of another major alternative payment policy proposal aiming to improve the value of care received by Medicare beneficiaries being treated for cancer. In contrast to the voluntary OCF program, the proposed Radiation Oncology (RO) model, announced in July 2019, would be mandatory and affect payment for 40% of the radiation therapy volume provided to Medicare beneficiaries nationwide, if finalized.4

The model proposes a fixed prospective payment, which includes both professional and technical components, that would vary based on 17 cancer types. Early analysis suggests that this model may incentivize more efficient treatment schedules, and the final rule is expected in late 2019 or early 2020.

CMS’ goals of reducing care costs and improving care quality are evident through the proposed OCF and RO models. For maximum provider engagement in both oncology payment models, it is imperative that CMS’ payment models continue to make adjustments that do not penalize historically efficient providers and create value-based innovators across the continuum of care. As providers consider their participation in these programs, they should be aware that frequent and robust data and appropriate quality measurement are critical pieces of a successful program. Additionally, we at Archway encourage providers considering the models to engage with CMS during the comment periods to help the agency build models that align incentives with high-quality patient care.

AUTHOR INFORMATION
Keely Macmillan, MPH, a senior vice president of Policy and Solutions Management at Archway Health. A recognized expert in alternative payment models, she has more than 12 years of healthcare experience in guiding specialty providers to success in accountable care organizations (ACOs), bundled payments, value-based purchasing, and MACRA Quality Payment Program.

ABOUT ARCHWAY HEALTH
Archway Health works with providers and employers to design and execute care and risk management initiatives that improve care and reduce costs. Archway is currently working with leading healthcare providers participating in risk-based contracts including bundled payment programs under the Center for Medicare and Medicaid Innovation such as BPCI Advanced, OCM, and the Comprehensive Care for Joint Replacement model. Archway also works with Medicare and commercial ACOs, self-insured employers, and commercial payers. To support ✓
ONCOLOGY CARE FIRST: COMMENTARY

PATEL: The suspense ended November 1, 2019, when the Center for Medicare & Medicaid Innovation (CMMI) unveiled a request for information (RFI) regarding Oncology Care First (OCF), a proposed successor model that would build on the lessons from the Oncology Care Model (OCM), as well as other stakeholders, designed a new model pretty much along the same line of what it is now. People are worried about what is going to happen after 5 years. What will happen once the summer of 2020 comes and OCM is kind of over? And when I saw the OCF model, I was happy. There is a little skepticism because CMS had scheduled a listening session for Monday [November 4, 2019]. Now, when there is an announcement from CMMI on Friday afternoon at 4 p.m. [November 1, 2019], the first reaction from many of my colleagues was "Oh, so they didn’t want to give us time to ask questions." And I put it differently. I said, "Look, they actually designed the model. We asked for an extension for deciding whether to move to a side risk."

The interview is edited slightly for clarity.

PARTICIPANTS IN THE ONCOLOGY CARE MODEL (OCM) have speculated greatly about what will come after the 5-year pilot program ends on June 30, 2021.¹ The suspension ended November 1, 2019, when the Center for Medicare & Medicaid Innovation (CMMI) unveiled a request for information (RFI) regarding Oncology Care First (OCF), a proposed successor model that would build on the lessons learned from OCM. When the RFI was released, CMMI already had scheduled a listening session for November 4, 2019, on the future of the OCM, and the short comment period left some stakeholders uneasy. The original 3-week comment period was extended to December 13, see Cover.

But Kashyap Patel, MD, the chief executive officer of Carolina Blood and Cancer Care Associates—a leading OCM practice—and associate editor of Evidence-Based Oncology (EBO), said he’s optimistic. As cochair of the Payment Reform Committee for the Community Oncology Alliance, Patel took part in the listening session with CMMI’s Christina Ritter, director of the Patient Care Models Group, as well as Lara Strawbridge and Hillary Cavanaugh, who are developing the successor model for CMMI. A few days later, Patel shared his early thoughts on the OCF with EBO.

EBO: Everyone has been waiting to see what will happen with the OCM as we look toward the end of the 5-year model. What do you think have been its biggest successes?

PATEL: That’s a very nice question. You’ve touched my heart, because I always believed we have the resources, technology, and intelligence to shift care from volume to value—and the OCM was the primer for that. There has been a large learning curve over the past 3 years. After the model was announced, we had 197 practices become a part of that. It took a learning curve of about 2 years, so far, for everyone to figure out what was expected of us, but now almost 80% of practices have reached success in addressing the benchmark prices [for cancer therapies], as well as improvement in the quality of care. So, the OCM has really allowed us to explore the road map to success in the transition from volume to value.

EBO: There was an element of surprise when CMMI released the RFI for Oncology Care First. Can you discuss the nature of the RFI and your initial reaction?

PATEL: It was very interesting. I was speaking on 2-sided risk at the Association of Community Cancer Centers conference in Orlando, Florida, in the last session. I was talking about the OCM and the future of the OCM, and we also had Alexander Chong, PhD, from CMMI, speaking right after I was done. And as I headed out of the room, I saw this [news] flash saying that CMMI had announced the RFI for Oncology Care First. So, it was a surprise, but it was a pleasant surprise for me. I am an eternal optimist. As an oncologist, I deal with the chance of 15% to 20% survival every day of my life, and so to see something like OCF coming out on Friday afternoon made my weekend. The reason is because we’re all worried about what is going to happen after 5 years. We’ve made a substantial improvement in the way we are dealing with care, but it’s coming with a price—we’ve had new employees, we’ve changed the way we work; [there are] new technology investments, new CT [computed tomography] scan machines. And when I look at all the investment, I was getting anxious [to the point] where I was losing sleep: What will happen once the summer of 2020 comes and OCM is kind of over? And when I saw the OCF model, I was happy.

There is a little skepticism because CMS had scheduled a listening session for Monday [November 4, 2019]. Now, when there is an announcement from CMMI on Friday afternoon at 4 p.m. [November 1, 2019], the first reaction from many of my colleagues was ’Oh, so they didn’t want to give us time to ask questions.’ And I put it differently. I said, ’Look, they actually designed the model. We asked for an extension for deciding whether to move to a 2-sided risk.’

One concern that everyone had was the short turnaround time for the comment period [later extended]. From the time they announced the model, there is a 3-week timeline. People are getting ready for travel, so these were some of the elements of surprise. But I still feel that there has been a genuine intention on the part of CMMI, as well as the team, to consider what has progressed...
Stephen M. Schleicher, MD, MBA, Addresses “Accountability Versus Control” in Oncology Care First

An Interview With Mary Caffrey

The interview is edited slightly for clarity.

ON OCTOBER 31, 2019, authors from Tennessee Oncology, OneOncology, and Tuple Health published an article in JAMA Oncology that offered a stunning conclusion: Even if a practice in the Oncology Care Model (OCM) compiled precisely with current guidelines from the National Comprehensive Cancer Network (NCCN) for meta-static non–small cell lung cancer and did everything right, drug costs would make it impossible to meet the financial targets spelled out in the model.1 The authors offered a solution: Instead of being judged against unattainable benchmarks, OCM practices should be measured based on their adherence to clinical pathways or ability to document why a pathway didn’t make sense for a particular patient. Almost on cue, the next day, the Center for Medicare & Medicaid Innovation (CMMI) released its proposal for Oncology Care First (OCF), the would-be successor to the OCM.2 One of the paper’s authors, Tennessee Oncology’s Stephen M. Schleicher, MD, MBA, was pleased to see that OCF reflected some of the issues he had his colleagues had discussed. Schleicher, who also serves as medical director for value-based care for OneOncology, a network that includes 242 providers, discussed the findings and CMMI’s proposal with Evidence-Based Oncology® (EBO):

EBO: Can you discuss your concerns with ePROs?

SCHLEICHER: I’m a medical oncologist at Tennessee Oncology; we are part of OneOncology, where I am chair of the Quality and Value Committee. I’ve been very passionate about value-based payment for the past 5 to 6 years since the Affordable Care Act came out and, specifically, as an oncologist, when the OCM came to fruition.

Our experience with the OCM, most importantly, has been a learning experience. I think that’s one of the biggest benefits of the model and why it has been a voluntary pilot. We’re getting lots of information about how we’re doing in keeping patients out of the emergency room when we can and how we’re using hospice.

EBO: Is it appropriate to have caregivers take part in the ePRO initiative?

PATEL: Caregivers could be a critical part of ePROs, but if patients have flip phones, then I don’t expect caregivers will have smart phones, either. We’ve talking about patients living paycheck to paycheck. They don’t have secondary insurance. They don’t have transportation. So, for them to have technology and pay $100 a month for access to the internet may be too much to expect. But we definitely would work with them, or our employee would work with them, to figure out how to do the ePRO. Or, maybe at some stage, we could have that done at a home visit, taking the technology along with creating a temporary hot spot to ensure that we fulfill the expectation. At the same time, we want to have some sort of balance between the expectation of the ePRO and what we can deliver.

EBO: What other takeaways did you have from the listening session?

PATEL: I was elated to see the enthusiasm among my colleagues—with skepticism. Whenever government comes in with some program, there is always some skepticism. But on the whole, I see an environment of collaboration, a cooperative and conducive environment to improve the quality of care for cancer patients.

There’s also an element of risk they expect us to take—small downside risk. And although that could be a matter of concern for many practices, when you look at the alternate path, the MIPS [Merit-based Incentive Payment System] track, MIPS has a 9% downside going from 2021 onward anyway.2 So, with either track, you have risk involved.

REFERENCES


Stephen M. Schleicher, MD, MBA, Addresses “Accountability Versus Control” in Oncology Care First

An Interview With Mary Caffrey

EBO: During the listening session, it appeared that CMMI tried to incorporate feedback from oncologists about appropriate ways to hold practices accountable for drug costs. Can you discuss areas where OCF reflects provider feedback?

PATEL: Absolutely. As soon as Lara Strawbridge said they were incorporating ePROs, my eyes went all over—I said, “I have patients who don’t have a smartphone. They still use a flip phone.” They live in areas where there aren’t even cell phone towers. Depending on the access to the technology, the ePRO reporting could be quite variable. At the same time, I want to be sure we respect technology, so our suggestion and request to CMMI—and we will be commenting on this, as well—will be to collect the ePROs at the point of care, when the patient comes to the clinic. We would invest more in the technology; we could buy some iPads so our employees could sit down with the patients to help them [record responses]. But we don’t want to make it very burdensome. Patients are sick. They have many more issues. To ask them to answer a hundred questions [at every appointment] may make them very tired. So, we want to create a balance between the expectations of the technology and dissemination of knowledge, and at the same time respect the patients’ ability and capacity to work with us.

EBO: Is it appropriate to have caregivers take part in the ePRO initiative?

PATEL: Caregivers could be a critical part of ePROs, but if patients have flip phones, then I don’t expect caregivers will have smart phones, either. We’re talking about patients living paycheck to paycheck. They don’t have secondary insurance. They don’t have transportation. So, for them to have technology and pay $100 a month for access to the internet may be too much to expect. But we definitely would work with them, or our employee would work with them, to figure out how to do the ePRO. Or, maybe at some stage, we could have that done at a home visit, taking the technology along with creating a temporary hot spot to ensure that we fulfill the expectation. At the same time, we want to have some sort of balance between the expectation of the ePRO and what we can deliver.

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REFERENCES


ONCOLOGY CARE FIRST: PROVIDER PERSPECTIVES

over the past 3 years to accommodate continuation of the model.

EBO: During the listening session, it appeared that CMMI tried to incorporate feedback from oncologists about appropriate ways to hold practices accountable for drug costs. Can you discuss areas where OCF reflects provider feedback?

PATEL: OCF is built on the success of the OCM as a pilot experiment. One of the challenges we had was patient attribution—we did not know when it was going to happen. In the OCF model, CMMI has promised us they will be updating [attribute data] every month so there will not be an element of surprise. Second, we were struggling with the drug costs. For example, the newer therapies, such as immunotherapies, could be much higher compared with benchmark prices, and they’ve actually looked at novel therapies in a much more robust way. And the third thing was the trend factor—the cancer-specific trend factor. [These are] 3 big elements that we’ve always been struggling with in the original model, and CMMI has promised and considered how they will adjust the pricing model based on these 3 factors.

EBO: A point that you raised during the listening session, with support from Barbara McNeney, MD, who developed the COME HOME model, was the concern about the handling of electronic PROs [patient-reported outcomes]. Disbursement of technology among cancer patients is very uneven. Can you discuss your concerns with ePROs?
We’ve had the opportunity to get rewarded through the care-management fees to provide nurse navigators, to help be the bridge between when the patient is in clinic and when the patient is at home. We’ve learned how to continue that communication and help direct patients to the clinic for fluids instead of to the emergency (department), to help assess a patient’s pain and act quickly before the pain gets out of control—similarly with nausea and constipation. So, we’ve been able to, through the resources provided from Medicare as part of the OCM, hire some additional staff to help with that.

Staff is one thing; secondly, with the analytic capabilities we’ve been encouraged to develop through our partners with Flatiron Health and now with OneOncology, as I mentioned, an understanding of our utilization patterns and how they compare with our peers’, both within the Oncology Care Model and without. Those are some huge benefits of the model, and one of the most exciting aspects of the model involves all we have learned to improve the care we’re delivering to our patients.

EBO: In your recent paper in JAMA Oncology,1 one of the central points you and your co-authors make is that practices should be held accountable for adhering to clinical pathways or documenting good reasons the pathway does not make sense. How did you arrive at that conclusion?

SCHLEICHER: So, it’s a great question. The impetus for putting this paper together was the whole issue of accountability versus control. As oncologists, we want to be accountable for things we do incor rectly, of course—even if that’s not on purpose. But delivering a more expensive chemotherapy to a patient when there’s a better option, using an emergency room instead of a clinic for things that could be handled outpatients—those are things we can be accountable for, that we can control, and we should be accountable for. But there also are aspects of cancer care that we have no control over, and the main thing there—the elephant in the room—is the price of drugs.

New drugs have tremendous benefit for patients. We want to be able to give new drugs to our patients. Immunotherapy is really the big thing that has boomed since the start of the OCM. But those drugs that have good benefits also have high price tags, and we want to make sure we can give those drugs to patients without being penalized, because in the current OCM, the total cost of drug use is something we are accountable for and could be penalized for.

What we wanted to do with the paper and this research is understand how well the OCM is incorporating the new prices of drugs into their expected costs of treating cancer patients. We looked at lung cancer…The field has [advanced] even since the time of the data that we looked at for this paper. But since the start of the OCM, the immunotherapy made its way into the second-line treatment of metastatic non–small cell lung cancer with both Keytruda (pembrolizumab) and Opdivo (nivolumab), which both have survival benefits. We thought that was a good opportunity to look and see if, when we used these drugs correctly—which we can control—we are still over target on what we should be spending, and if it’s due to the price alone, we cannot control that. And that’s a problem with a value-based care model—trying to improve the quality of care and the cost of care if we can’t control that.

So, that’s why we looked at lung cancer. We looked at all our cases where Medicare told us we had spent more than expected, and within that, where we had prevented everything that was the goal of the OCM. [We looked at cases where] we prevented emergency [department] visits, we prevented hospitalizations, postacute care, inappropriate chemotherapy at end of life—all these aspects that we can control and one should be able to prevent. We saw that in many of our cases—over half—we had done all that, but we were still over target because we had used either Keytruda or Opdivo in the second-line setting for metastatic non–small cell lung cancer. That was NCCN compliant at the time and is still standard of care, although we now often use immunotherapy first line. We found in that group of patients that we were over target for using the right drug at the right time for patients that deserved to have that drug; yet the model, despite Medicare’s best attempts, couldn’t account for that, and that is what we are trying to communicate with the paper.

Our conclusion was that we were pathway or guideline concordant, which is what we can control and that’s what we should be doing; the cost was higher because of the price, which we can’t control. So maybe the pathway concordance—following pathways we can all agree on—is a better measure of us using the right drug than the cost of care itself, from a drug perspective.

EBO: And the data you present were consistent across the practices that you surveyed?

SCHLEICHER: Exactly. We have 30 clinics in Tennessee Oncology right now—OneOncology has over 100—but we were looking at Tennessee Oncology, and this was not clinic specific; this was across all our providers at the different clinical sites.

EBO: The day after your paper appeared, CMMI released a request for information on a model that is being called Oncology Care First, or OCF, which will be the successor to OCM when it expires in 2021. What are your observations so far about OCF?

SCHLEICHER: OCF, I think, is an example of Medicare being very thoughtful—of recognizing that we need to change the way care is delivered but also recognizing that cancer is a very difficult disease because it is very heterogeneous—every patient with cancer is different, every cancer is different. We have high costs of care both from utilization and drugs. So, I think they tried to come up with a thoughtful model to do this.

There were 2 components of the OCF model that I think are definite improvements from OCM that relate to our paper in terms of the accountability versus control. First, how they calculate the expected cost of treating cancer care and how drug costs are incorporated into that; there are 2 mechanisms for that through the trend factor that accounts for overall implementation of healthcare costs, and the novel therapy adjustment, which is how a practice is using new drugs that have been FDA approved compared with their peers.

In the OCM, they applied this across all cancer types and all patients in conglomerate; OCF, they will look at the specific cancer itself. When a new drug or a new indication comes to that disease, they will try to account for that change at the [level of the] disease itself—which, hopefully, improves the accuracy of predicting the cost of care as healthcare standards of care change in oncology. That’s a benefit and shows that Medicare was listening to us as we all provided feedback during the OCM, and it is clearly very relevant to the paper we just published in JAMA Oncology.

A second improvement is how providers should be accountable for some of the low-risk cancers, such as low-risk breast, low-risk bladder, and low-risk prostate. Let’s take low-risk breast cancer—that could be a patient who had surgery, chemotherapy, and radiation therapy 4 to 5 years ago but still requires antiestrogen therapy—a hormonal pill. In that case, the provider might be seeing the woman every 6 months to prescribe that pill; standard of care might be a mammogram once a year for a patient who still has her breasts intact, with an exam. In the current setting, if we are treating a patient like that but they go to the emergency room because they have a stroke or because they need a hip replacement or they have a heart attack—something completely unrelated to their disease—we are still accountable for that care under the current OCM. They have corrected this in the current OCF by removing these patients from the accountability portion of the total cost of care, such that we are more accountable for patients for whom we are providing intensive chemotherapy, seeing them regularly and really are responsible for their care, versus patients we are seeing every 6 months who have other unrelated health problems that could throw off our ability to succeed in the value-based care model.

EBO: That would seem to make sense. Do you have any other observations as you move forward with alternative payment models?

SCHLEICHER: It’s important for groups to be in these models, even if they are voluntary, just to learn about how they are doing compared with their peers and find opportunities for improvement. And as long as groups can publish on these matters and make it known to their other colleagues across the country interested in improving the value of care of cancer—if we can communicate that through publications such as ours (in JAMA Oncology), through conferences, through Medicare, to help these models get better over time, that’s really how we succeed: all of us coming together versus working independently.●

REFERENCES
Indications
IBRANCE® (palbociclib) 125 mg capsules is indicated for the treatment of adult patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer (MBC) in combination with:
- an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men, or
- fulvestrant in patients with disease progression following endocrine therapy

Supported by compelling Phase 3 evidence and unmatched experience in its class,
IBRANCE combination therapy has helped change the story of HR+/HER2- MBC

Important Safety Information
Neutropenia was the most frequently reported adverse reaction in PALOMA-2 (80%) and PALOMA-3 (83%). In PALOMA-2, Grade 3 (56%) or 4 (10%) decreased neutrophil counts were reported in patients receiving IBRANCE plus letrozole. In PALOMA-3, Grade 3 (35%) or Grade 4 (11%) decreased neutrophil counts were reported in patients receiving IBRANCE plus fulvestrant. Febrile neutropenia has been reported in 1.8% of patients exposed to IBRANCE across PALOMA-2 and PALOMA-3. One death due to neutropenic sepsis was observed in PALOMA-3. Inform patients to promptly report any fever.

Monitor complete blood count prior to starting IBRANCE, at the beginning of each cycle, on Day 15 of first 2 cycles and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Please see Important Safety Information throughout, followed by Brief Summary of Prescribing Information.
Important Safety Information (cont.)

Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with CDK4/6 inhibitors, including IBRANCE when taken in combination with endocrine therapy. Across clinical trials (PALOMA-1, PALOMA-2, PALOMA-3), 1.0% of IBRANCE-treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 2 or 3, and no fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g., hypoxia, cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed pneumonitis, interrupt IBRANCE immediately and evaluate the patient. Permanently discontinue IBRANCE in patients with severe ILD or pneumonitis.

Please see Important Safety Information throughout, followed by Brief Summary of Prescribing Information.
STRENGTH IN FIRST LINE: IBRANCE + LETROZOLE
In a 2:1 randomized, double-blind, Phase 3 trial of postmenopausal women with ER+/HER2- MBC (N=666)2,7
- IBRANCE + letrozole demonstrated a compelling 10-month mPFS improvement vs placebo + letrozole
  - Investigator-assessed PFS was the primary endpoint
  - 9.5 months mPFS (n=347) vs 4.6 months mPFS with placebo + letrozole (n=174); (95% CI: 9.2-11.0 vs 3.5-5.6); HR=0.46 (95% CI: 0.36-0.59); P<0.0001
  - Number of PFS events: 194 (43.7%) with IBRANCE + letrozole vs 137 (61.7%) with placebo + letrozole
- ORR (secondary endpoint): 33.3% (95% CI: 29.9-36.7) with IBRANCE + letrozole vs 11.4% (95% CI: 8.9-14.9) with placebo + letrozole
- At the time of final analysis of PFS, OS (secondary endpoint) data were not mature. Patients will continue to be followed for the final analysis

STRENGTH IN FIRST LINE OR LATER: IBRANCE + FULVESTRANT
In a 2:1 randomized, double-blind, Phase 3 trial of women with HR+/HER2- MBC whose disease progressed following endocrine therapy (N=521)3,6
- IBRANCE + fulvestrant doubled mPFS vs placebo + fulvestrant
  - Investigator-assessed PFS was the primary endpoint
  - 4.6 months mPFS (n=317) vs 9.5 months mPFS with placebo + fulvestrant (n=184); (95% CI: 6.2-17.3) with placebo + fulvestrant (IBRANCE + fulvestrant n=317; placebo + fulvestrant n=184)
  - A final OS (secondary endpoint) analysis was conducted with 311 events (~60% of trial population) having occurred. These data show a numerical difference in favor of IBRANCE + fulvestrant vs placebo + fulvestrant that did not reach statistical significance2,4
  - Median OS was 14.9 months (95% CI: 28.8-40.0) with IBRANCE + fulvestrant vs 28.0 months (95% CI: 23.6-34.6) with placebo + fulvestrant (HR=0.81 [95% CI: 0.64-1.03]; P=0.09); a difference of 6.9 months
  - This difference in median OS was similar to the improvement in mPFS previously seen with the addition of IBRANCE to fulvestrant in PALOMA-3

Get the results for updated analyses from your IBRANCE representative or at IBRANCEhcp.com

Important Safety Information (cont.)

The most common adverse reactions (≥20%) of any grade reported in PALOMA-2 for IBRANCE + letrozole vs placebo plus letrozole were neutropenia (60% vs 65%), infections (60% vs 65%), diarrhea (26% vs 27%), rash (25% vs 19%), asthenia (17% vs 12%), pyrexia (16% vs 10%), nausea (15% vs 11%), vomiting (13% vs 8%), and anemia (13% vs 5%)
The most frequently reported Grade ≥3 adverse reactions (≥5%) in PALOMA-2 for IBRANCE + letrozole vs placebo plus letrozole were neutropenia (66% vs 2%), leukopenia (25% vs 0%), infections (7% vs 5%), and anemia (5% vs 2%)
Lab abnormalities of any grade occurring in PALOMA-2 for IBRANCE + letrozole vs placebo plus letrozole were decreased WBC (97% vs 25%), decreased neutrophils (95% vs 20%), anemia (78% vs 42%), decreased platelets (63% vs 14%), increased aspartate aminotransferase (52% vs 34%), and increased alanine aminotransferase (43% vs 50%)
The most common adverse reactions (≥20%) of any grade reported in PALOMA-3 for IBRANCE plus fulvestrant vs placebo plus fulvestrant were neutropenia (83% vs 4%), leukopenia (53% vs 5%), infections (41% vs 31%), fatigue (41% vs 25%), anemia (34% vs 28%), diarrhea (34% vs 19%), thrombocytopenia (23% vs 0%), vomiting (9% vs 13%), asthenia (18% vs 6%), rash (17% vs 6%), decreased appetite (16% vs 8%), and pyrexia (13% vs 5%)
The most frequently reported Grade ≥3 adverse reactions (≥5%) in PALOMA-3 for IBRANCE plus fulvestrant vs placebo plus fulvestrant were neutropenia (66% vs 16%) and leukopenia (31% vs 2%)
IBRANCE COMBINATION THERAPY HAS HELPED CHANGE THE STORY OF HR+/HER2- MBC

Evaluated in a broad range of patients

**PALOMA-2:**
IBRANCE + letrozole
- First line (no prior lines of MBC therapy)
- Postmenopausal women
- 30-89 years of age (median=62)
- Visceral/nonvisceral/bone-only disease
- DFI: De novo metastatic, ≤12 months, >12 months
- With or without prior (neoadjuvant chemotherapy

**PALOMA-3:**
IBRANCE + fulvestrant
- First line or later (0 to ≥3 prior lines of MBC therapy)
- Pre-/peri-/postmenopausal women
- 30-88 years of age (median=57)
- Visceral/nonvisceral/bone-only disease
- DFI: ≤24 months, >24 months
- Up to 1 prior line of chemotherapy for MBC

In-practice experience

- 4+ YEARS since initial FDA approval
- 13,000+ PRESCRIBERS have chosen IBRANCE
- 100,000+ PATIENTS prescribed IBRANCE

**Intraperitoneal experience**

**Important Safety Information** (cont.)

Lab abnormalities of any grade occurring in PALOMA-3 for IBRANCE plus fulvestrant vs placebo plus fulvestrant were decreased WBC (99% vs 26%), decreased neutrophils (96% vs 14%), anemia (78% vs 49%), decreased platelets (62% vs 10%), increased aspartate aminotransferase (45% vs 48%), and increased alanine aminotransferase (36% vs 34%).

Avoid concurrent use of strong CYP3A inhibitors. If patients must be administered a strong CYP3A inhibitor, reduce the IBRANCE dose to 75 mg. If the strong inhibitor is discontinued, increase the IBRANCE dose (after 3-5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Grapefruit or grapefruit juice may increase plasma concentrations of IBRANCE and should be avoided. Avoid concomitant use of strong CYP3A inducers. The dose of sensitive CYP3A substrates with a narrow therapeutic index may need to be reduced as IBRANCE may increase their exposure.

For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg.

The pharmacokinetics of IBRANCE have not been studied in patients requiring hemodialysis.

References:

Please see Important Safety Information throughout, followed by Brief Summary of Prescribing Information.
Brief Summary of Prescribing Information

**IBRANCE® (palbociclib) capsules, for oral use**

**Initial U.S. Approval: 2015**

**INDICATIONS AND USAGE**

IBRANCE is indicated for the treatment of adult patients with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men, or
- fulvestrant in patients with disease progression following endocrine therapy.

**DOSAGE AND ADMINISTRATION**

**Recommended Dose and Schedule:** The recommended dose of IBRANCE is 250 mg capsules taken orally once daily for 21 consecutive days followed by 7 days of treatment to complete a cycle of 28 days. IBRANCE should be taken with food.

Adhere the recommended dose of an aromatase inhibitor when given with IBRANCE. Please refer to the Full Prescribing Information for the aromatase inhibitor being used.

**Dose Interruption:** If a patient misses a dose, the patient should take the missed dose as soon as possible and continue with the oral IBRANCE daily dose at the next scheduled time. The next prescribed dose should be taken at the usual time. IBRANCE capsules should be swallowed whole (do not chew, divide, crush, or suck on the capsule or tablet). Capsules or tablets that are broken, cracked, or otherwise not intact should not be used.

**Precautions Towards Treatment with the Combination BIARANCE plus fulvestrant therapy should also be treated with limiting hormone-releasing hormone (LHRH) agonists according to current clinical practice guidelines**

**Dose Modifications:** If dose reduction is required, the first recommended dose reduction is to 100 mg bid; and the second dose reduction is to 50 mg bid. If further dose reductions below 75 mg bid is required, discontinue the treatment.

**Dose and Management – Hematologic Toxicities**

- Maximal complete blood counts prior to the start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the 2nd cycle, and as clinically indicated.
- For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 4 cycles, monitor complete blood counts for subsequent cycles every 4 to 6 months, prior to the beginning of a cycle and as clinically indicated.

**CTCAE Grade Dose Modifications**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dose Modifications</th>
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<tbody>
<tr>
<td>1 or 2</td>
<td>No dose adjustment is required.</td>
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<tr>
<td>3</td>
<td>Dose reduction to 100 mg bid.</td>
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<tr>
<td>4</td>
<td>Dose reduction to 50 mg bid.</td>
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**Cautions According to CTCAE 4.0**

- **CTCAE—Common Terminology Criteria for Adverse Events.** All non-fatal events are reported.
- **a** Relates to all hematologic toxicities except lymphopenia toxicities associated with clinical events, e.g., opportunistic infections.
- **b** Non-hematologic toxicity of Grade ≥3 non-hematologic toxicity is reported.
- **c** Grade 4 non-hematologic toxicity is reported.
- **d** Grade 5 non-hematologic toxicity is reported.
- **e** Dose modification as indicated for patients with prolonged (>1 week) grade 3 or 4 neutropenia.
- **f** Grade 3 non-hematologic toxicity of Grade 3 non-hematologic toxicity is reported.
- **g** Grade 4 non-hematologic toxicity is reported.
- **h** Grade 5 non-hematologic toxicity is reported.

**Dosing Forms and Strengths**

- 125 mg capsules: opaque blue gelatin capsules, size 0, with carved cap and body. PBC 125 as the body.
- 100 mg capsules: opaque blue gelatin capsules, size 1, with carved cap and light orange body. PBC 100 on the cap. PBC 100 on the body.
- 30 mg capsules: opaque blue gelatin capsules, size 5, with carved cap and black body. PBC 30 on the cap. PBC 30 on the body.
- Printed with white ink “Pharm” on the cap, “PBC 75” on the body.

**CONTRAINDICATIONS:**

- Hypersensitivity to palbociclib.

**WARNINGS AND PRECAUTIONS**

- **Neutropenia:** Neutropenia is the most frequently reported adverse reaction in Study 1 (PALOMA-2) with an incidence of 85% and Study 2 (PALOMA-3) with an incidence of 83%. A Grade 5 neutropenia rate of 21% in Study 1, due to neutropenic counts, was reported in 6% of patients receiving IBRANCE plus letrozole in Study 1, and 19% of patients receiving IBRANCE plus fulvestrant in Study 2. In Study 1 and 2, the median time to first episode of any grade neutropenia was 15 days and the median duration of Grade 3 or 4 neutropenia was 7 days.
- Maximal complete blood counts prior to starting IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated. Dose interruptions, dose reductions, or delays in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Palbociclib has been reported in 1.8% of patients exposed to IBRANCE across Studies 1 and 2. One death due to neutropenic sepsis was observed in Study 2. Physicians should inform patients to promptly report any episodes of fever or infection.睡前使用IBRANCE或与饭后使用IBRANCE之间的选择不会影响IBRANCE的生物利用度。IBRANCE未报告对其他已批准的CDK4/6抑制剂有相互作用。IBRANCE与恩曲他滨之间的相互作用发生在用于治疗乳腺癌的联合治疗中。
Laboratory Abnormalities in Study 2

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Based on findings from animal studies, IBRANCE can cause embryofetal toxicity. In animals, IBRANCE exposure is known to cross the placenta at doses up to 300 mg/kg/day. In rats, exposure at doses up to 20 mg/kg/day in rabbits, there was an increased incidence of skeletal variations, including small sphenoid wings, in the offspring. In dogs in repeat-dose toxicology studies up to 39 weeks duration.

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses up to 30 mg/kg/day with maternal systemic exposures approximately 4 times the human exposure (AUC) at the recommended dose.

In embryo-fetal development studies in rats and rabbits, pregnant animals received doses up to 300 mg/kg/day and 25 mg/kg/day, respectively, during the period of organogenesis. The maternally toxic dose of 30 mg/kg/day was toxic to the rat, resulting in reduced body weights. At doses of 100 mg/kg/day in rat, there was an increased incidence of a skull dysplasia (increased incidence of 0.3% at the seventh cervical vertebra) at the maternally toxic dose. Based on findings from animal studies and its mechanism of action, IBRANCE can cause embryofetal toxicity. In humans, the risk of adverse events with IBRANCE use beyond the reproductive window is unknown.

The safety of IBRANCE (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in Study 2. IBRANCE was administered for 21 days on a 21-day cycle for 3 cycles. Study 2 was initiated on July 13, 2010, and completed on July 30, 2012. Patients received placebo plus fulvestrant or IBRANCE plus fulvestrant. Study 2 included patients with HR-positive, HER2-negative advanced or metastatic breast cancer who had progressed after 1 to 2 previous endocrine therapies with disease progression occurring since last treatment. The median number of previous endocrine therapies was 2.

In Study 2, 1131 patients were randomly assigned to receive IBRANCE plus fulvestrant or placebo plus fulvestrant. The median age of patients was 56 years, with 68% female and 32% male. The median Karnofsky performance score was 80%.

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

In a fertility and early embryonic development study in female rats, palbociclib was administered orally to pregnant rats at doses of 29, 147, and 300 mg/kg/day for 5 days from gestation day 5 to 10. Based on findings from animal studies and its mechanism of action, IBRANCE can cause embryofetal toxicity. In humans, the risk of adverse events with IBRANCE use beyond the reproductive window is unknown.

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CONTINUED FROM COVER

For more than 45 years, the International Association for the Study of Lung Cancer (IASLC), with our membership of nearly 6500 lung cancer experts worldwide, has been working tirelessly toward a world without lung and other thoracic cancers. The task is immense as lung cancer is, and to add strength to our efforts we recently joined with other leading organizations in the lung cancer space to create a powerful force for change: The Lung Ambition Alliance (“The Alliance”).

The Alliance unites the IASLC, the Global Lung Cancer Coalition, AstraZeneca, and Guardant Health with a common goal: to one day eliminate lung cancer as a cause of death. To achieve this bold goal, we will start by doubling the 5-year survival in lung cancer by 2025.

Improving survival rates in lung cancer is both complicated and multifactorial; thus, our plans must be varied and dynamic to address each barrier to ensure optimal outcomes. We need to move beyond existing prevention efforts to target every point in the patient journey with innovative and effective strategies. This includes establishing early diagnosis through broader screening guidelines, developing more innovative medicines, and ensuring the best quality of care and support for patients and families.

The Alliance has identified 3 priority areas that align with critical points in the patient journey, and we are already undertaking several flagship projects, focused on these priority areas, to create positive change in the lung cancer landscape.

Increasing Lung Cancer Screening and Early Diagnosis

Late diagnosis is a key reason that survival rates for lung cancer are so poor. Forty percent of patients are diagnosed after cancer has already spread beyond the lung. To significantly shift the survival curve, we must diagnose and treat patients at earlier stages of disease. Because early-stage disease is often asymptomatic, this can be done only by improving lung cancer screening.

The IASLC has focused on improving lung cancer screening for some time. In October 2018, we issued a statement supporting the findings of the Dutch–Belgian NELSON (Nederlands-Leuven Longkanker Screenings Network) Randomized Lung Cancer Screening Trial7 and the National Lung Screening Trial (NLST).8 The landmark 2011 NLST was the first large-scale trial to show that lung cancer screening with low-dose computed tomography (LDCT) can significantly reduce mortality. The NLST enrolled more than 50,000 patients, aged 55 to 74 years, who were current smokers with >30 pack-years of cigarette smoking history or who had quit smoking in the past 15 years.10 Results showed that participants who received LDCT scans had a 20% lower risk of dying from lung cancer than participants who received standard chest x-rays, and 50% of lung cancers detected by LDCT were stage I disease.11,12

However, in addition to highlighting the obvious advantages of screening, the NLST also revealed flaws in real-world national screening programs.13 First, CT scanning is associated with a high rate of false-positive results. In the NLST, 24.2% of the results from the CT scans performed were positive, and more than 96% of nodules uncovered were later deemed to be false positives,14 causing unnecessary stress and concern to thousands of patients. In addition, for those patients who did test positive, further procedures were required to confirm the diagnosis, including additional scanning or a biopsy, which can be invasive and carry serious risks. Finally, perhaps the biggest barrier to large-scale screening programs is the limit that national insurance coverage and reimbursement policies place on which patients are eligible to receive screening.

For example, in the United States, guidelines were adopted by the US Preventive Services Task Force based on data from NLST, and lung cancer screening has been recommended since 2014. However, these guidelines have been enforced only in high-risk individuals (Table 1, SP384), which means that they are utilized by only about 8% of those dying from this disease annually.15

Outside the United States, few countries have screening policies. After reviewing the NLST results, many countries continued to wait for data from a study outside of the United States to confirm the findings before they considered implementing screening. Confirmation finally became available in 2018, when results from the 10-year follow-up of NELSON were presented at the IASLC 19th World Conference on Lung Cancer. With 15,822 participants, the NELSON trial was the largest-ever European lung cancer CT screening trial. The study was designed to determine the effect of stringent referral criteria and increasing screening intervals on the characteristics of screen-detected lung cancers. The study confirmed the findings of the NLST and helped to address key barriers to improving lung cancer screening.16

Prostate: 12.2% of men died from prostate cancer
Breast: 19.1% of women died from breast cancer
Colorectal: 19.1% of men died from colorectal cancer
Lung: 21.4% of men died from lung cancer

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FIGURE 1. Lung Cancer and Death

Approximately 1 in 5 cancer deaths are attributed to lung cancer.

questions, including how to minimize false positives. In NELSON, LDCT screening led to a 26% reduction in lung cancer deaths in men and a 39% reduction in women after 10 years, and it confirmed that we can increase the number of patients diagnosed with early-stage lung cancer. Compared with other trials, the screen-detected lung cancers of the NELSON trial were relatively more often diagnosed at stage I, when there is curative possibility, and less often at stage III-B-IV, when the prognosis has significantly worsened. Findings from NELSON are summarized in Table 2.15-16

We now have the data and insights we need to act and implement national-level LDCT screening programs for people at high risk for lung cancer. However, despite growing evidence from lung cancer CT screening studies, few countries, districts, or regions have implemented LDCT screening to facilitate detailed analysis of gathered CT data to improve the reliability of clinical decision support with CT screening, and to assist in the development of precise quantitative disease biomarkers.25 ELIC was developed in 2018 by the IASLC with the intention of creating a large, globally accessible, privacy-secured network of shared CT lung cancer images and associated biomedical data.21 In December 2018, the IASLC announced the completion of a 4-month pilot project which showed ELIC’s potential to bring significant improvements to lung cancer screening by creating a viable environment for the analysis of large collections of quality-controlled CT lung cancer images.29 Phase 2 of the project is currently underway, in which additional “data spokes” are being added to make the registry of images more robust and powerful, and quantitative algorithm experiments are being run on data from 6 sites. Once this is complete, ELIC will expand out to a fully operational system and conduct numerous experiments of the internationally curated data.

Delivering Innovative Medicine
We are at a critical moment in the fight against lung cancer. Medical innovations and an increased understanding of the underlying biology of lung cancer are already shifting what is possible in treatment. The key challenge now is to accelerate treatment advances for people with lung cancer today, and for the millions who will be diagnosed in the future. However, several barriers remain to be overcome.

First, it is important that patients receive a timely and accurate diagnosis. Barriers to accurate and timely lung cancer staging represent a lost opportunity to guide patients on the appropriate treatment path. The IASLC has led in the creation of lung cancer staging standards for years. With the support of The Alliance, the IASLC is working to standardize international lung cancer staging guidelines and deepen insights into disease progression. Insights from this effort will inform the 9th edition of the Tumor, Node and Metastasis staging system, the most common method for staging lung cancer, and will guide physicians in identifying the right treatment for the right patient at the right time.22-27

Secondly, testing for biomarkers plays an important role in guiding selection of patients for precision medicine therapies. However, currently, many patients who may be eligible for precision medicines, and the improved outcomes they may offer, are not being tested for biomarkers at diagnosis.28-29

The Alliance will champion initiatives focused on biomarker discovery and on improving access to high-quality diagnostic approaches like liquid biopsy, as well as the increased uptake of precision medicine approaches in earlier settings where there is greater potential for cure. We are currently exploring several projects in this area, including those that will investigate the validation of surrogate endpoints and identification of predictive biomarkers to accelerate the development of new treatments.

Third, the emergence of precision medicine is making prolonged clinical response a realistic goal of lung cancer therapy. To further improve lung cancer survival outcomes, however, we must explore the potential for precision medicines in earlier stages (stages I-III) where there is a greater chance of cure.20,22 As part of its Major Pathologic Response Project, The Alliance is working to validate surrogate endpoints and identify predictive biomarkers to accelerate the delivery of innovative medicines.26,29

Lastly, poor survival outcomes in lung cancer may also be tied to the disparity in lung cancer research funding compared with other cancer types (Figure 3).30,31 Lung cancer is consistently

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**TABLE 1.** Current Lung Cancer Screening Guidelines15

<table>
<thead>
<tr>
<th>Stage</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>Fourth</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>64.9%</td>
<td>75.9%</td>
<td>72.2%</td>
<td>60.9%</td>
</tr>
<tr>
<td>II</td>
<td>9.5%</td>
<td>6.1%</td>
<td>3.9%</td>
<td>15.2%</td>
</tr>
<tr>
<td>III</td>
<td>18.9%</td>
<td>13.7%</td>
<td>19.5%</td>
<td>10.8%</td>
</tr>
<tr>
<td>IV</td>
<td>6.8%</td>
<td>3.4%</td>
<td>3.9%</td>
<td>13.0%</td>
</tr>
</tbody>
</table>

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**TABLE 2.** Findings From NELSON16

<table>
<thead>
<tr>
<th>Stage</th>
<th>Current practice*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>26%</td>
</tr>
<tr>
<td>II</td>
<td>9%</td>
</tr>
<tr>
<td>III</td>
<td>25%</td>
</tr>
<tr>
<td>IV</td>
<td>40%</td>
</tr>
</tbody>
</table>

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**FIGURE 3.** Research Funding Does Not Reflect Lung Cancer Burden21

5.6% of global cancer research focuses on lung cancer and ~20% total cancer deaths.
underfunded relative to societal health cost and economic costs.\(^3\)

In the United States, funding for lung cancer research in 2016 was only about half that of breast cancer research.\(^2\) The National Cancer Institute's funding for lung cancer research was $321 million in 2016, compared with $545 million and $208 million for breast cancer research and colorectal cancer research, respectively.\(^3\)

The Alliance will work to improve awareness and understanding of lung cancer, to reduce stigma in the hope that this correlates to a level of public funding for lung cancer research that matches the urgency of the disease and the current promise of medical innovations.

At the IASLC 2019 World Conference on Lung Cancer in Barcelona in September 2019, the Alliance announced the official launch of an international survey, conducted by Ipsos MORI, which will invite general practitioners, lung cancer specialists, and the public from 7 countries across 3 continents to share their perceptions around lung cancer.

The survey will help generate insights and aid The Alliance in developing tailored patient solutions as well as advocacy initiatives. The survey will also establish a barometer by acting as a benchmark to help track the impact of Alliance programs over time. The results of this survey are expected in 2020.

**Improving Quality Care**

The Alliance's final priority area recognizes that people with lung cancer need support on their journey of care. We, as a lung cancer community, need to work with advocates and policymakers to deliver projects to address the healthcare challenges most urgent to patients. Patients need access to the multidisciplinary team they require to manage their condition; health systems and insurers need to have an urgency to act in them to provide patients with access to the best possible treatment.

To this end, The Alliance is committed to implementing benchmarking and quality improvement processes in the management of lung cancer. We will identify projects to ensure that patients have a better experience in their journey and achieve better outcomes. The Alliance has launched a new grants program, the Initiatives in Lung Cancer Care (ILC\(^2\)), to engage with the global community and encourage ambitious in-country solutions that can potentially transform patient care and improve survival rates in lung cancer. The ILC\(^2\) program is an open call, inviting registered patient organizations around the world to submit proposals for projects that can potentially transform patient care and improve survival within their home countries.\(^4\)

The program recognizes the high variation in lung cancer management around the world as well as the specific, localized barriers to quality care that must be considered when developing patient-centric solutions to address them.

The Alliance began accepting grant applications in November 2019 and will evaluate and select submissions in 2020 to meet the criteria for funding.

**Changing Lung Cancer Survival**

The Alliance is only a few months old, but the efforts of each individual partner go back decades.
Blood cancer therapies are rapidly improving.

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