SPECIAL ISSUE: **ADVERSE EVENTS** | FEATURING CONFERENCE COVERAGE: **ACCC** | **NCCN** | **COA**

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ALSO IN THIS ISSUE

DATA EMPLOYMENT AND AI IN CANCER CARE. At *AJMC*®'s Institute for Value-Based Medicine meeting in Dallas, Texas, presenters discussed how artificial intelligence (AI) holds the promise of helping oncologists predict outcomes such as which patients will need pain management and which ones are at risk of depression, SP146.

UPDATES FROM NCCN'S ANNUAL MEETING. During the National Comprehensive Cancer Network (NCCN) annual meeting, presenters provided various clinical and policy updates from recommendations for germline testing to advances in biosimilars, SP154.

PATEL

FROM TEAM BUILDING TO IMPLEMENTATION. Authors from Carolina Blood and Cancer Care Associates discuss how to take approaches learned in team building and use them in the Oncology Care Model, SP143.

NEW CLINICAL TRIAL GUIDANCE. FDA recently updated its oncology clinical trial guidance documents to expand inclusion to pediatric patients as well as patients with comorbidities, SP145.

APPROVAL FOR ATEZOLIZUMAB. FDA has granted accelerated approval for atezolizumab (Tecentriq), in combination with nab-paclitaxel (Abraxane) for the treatment of adults with unresectable locally advanced or metastatic triple negative breast cancer, SP168.

ADVERSE EVENT TRACKING

A Step in the Digital Direction: From Paper Logs to Electronic Data Capture

Nate Brown, BA; Evelyn Siu, BA; and Janet Donegan, ANP-BC, AOCN

RESEARCH DOCUMENTATION IS A critical aspect of running a clinical trial. Key patient information such as informed consent, adverse events (AEs), concomitant medications, and medical and surgical histories are collected and used to determine patient safety and efficacy as the trial proceeds. Ultimately, the sponsor may make decisions—ranging from modifying the dose of the investigational drug to closing the study due to AEs—based on the data collected.

Despite how critical this information is to a clinical trial, research documentation remains largely a cumbersome, paper-based process. The collection of paper research documentation, separate from the patient's medical chart, is often referred to as a "shadow chart"; this results in source documentation stored outside the patient's electronic health record (EHR). This information must be carefully tracked and transferred among all stakeholders who enter, edit, or sign off on any of these documents.

CONTINUED ON SP173

POLICY UPDATE

Providers, Industry Raise Concerns About CMS Plan for CAR T-Cell Reimbursement, Reporting on PROs

Mary Caffrey

ACADEMIC MEDICAL CENTERS AND a group representing community oncology practices have both raised concerns about CMS' proposed reimbursement plan for chimeric antigen receptor (CAR) T-cell therapy,[1,2] the individually manufactured gene treatments that are revolutionizing cancer care. The plan will be finalized next month, a year after the federal government launched a national coverage analysis (NCA) to determine how to pay for these lifesaving yet expensive cancer treatments.

CONTINUED ON SP178

ADVERSE EVENT MANAGEMENT

The Conundrum of Antibacterial Use in Neutropenic Patients Undergoing Chemotherapy for Hematologic Malignancy or HSCT

Sanjeet Singh Dadwal, MD

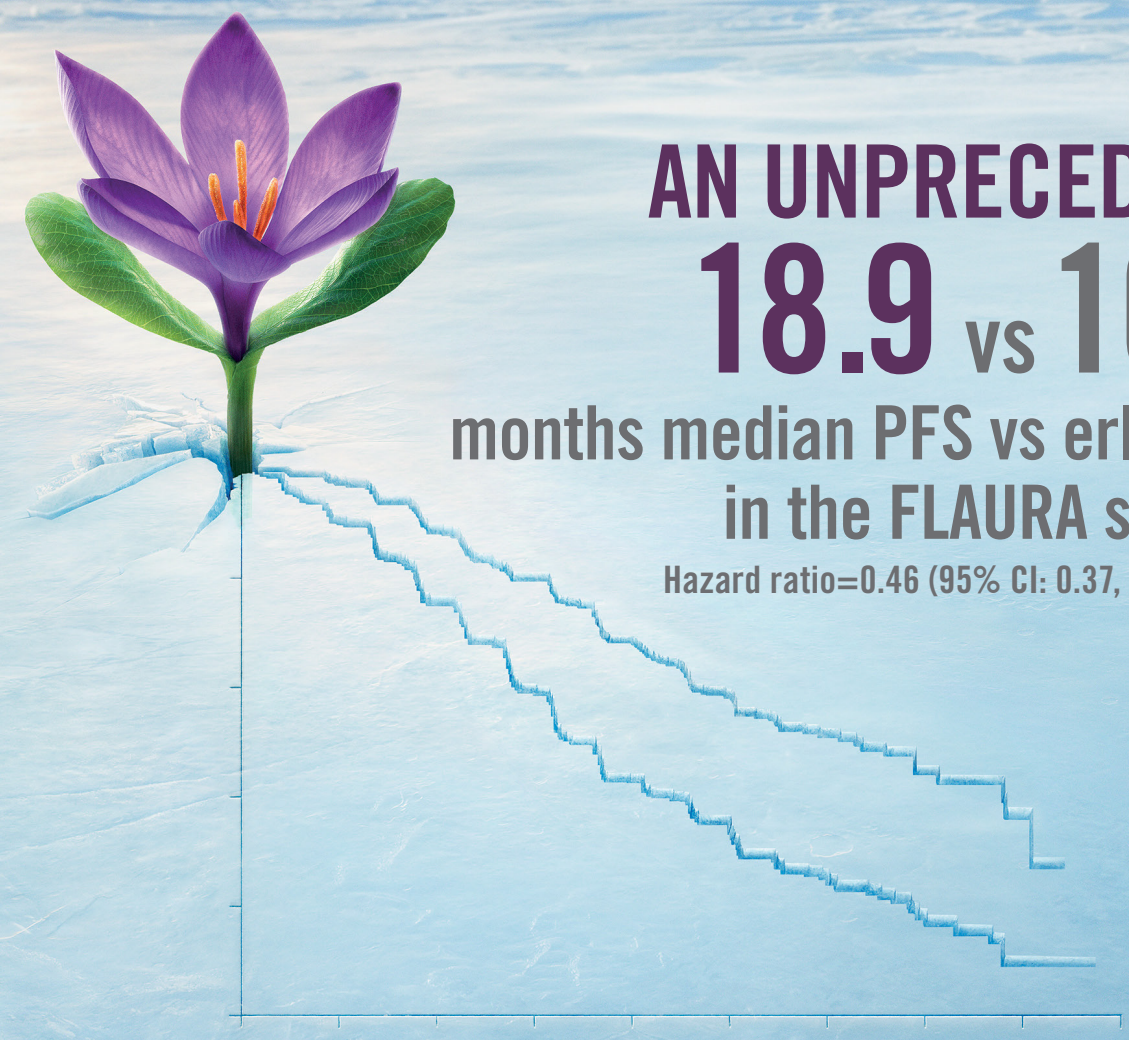
PATIENTS WITH HEMATOLOGIC MALIGNANCY (HM) who are undergoing chemotherapy or a conditioning regimen for hematopoietic stem cell transplant (HSCT) are at high risk of infection because of the severity and duration of neutropenia. Fever with neutropenia is a common presentation that suggests an infection leading to empiric antibacterial therapy. To prevent infection and thus the neutropenic fever, antibacterial prophylaxis, especially with fluoroquinolones, emerged as a common practice based on results of 2 randomized controlled trials published in 2005 that showed reduced incidence of fever and bacteremia despite lack of a mortality benefit.[1,2]

CONTINUED ON SP176

A white blood cell interacting with red blood cells.

FOR THE TREATMENT OF METASTATIC EGFRm NSCLC

FIRST-LINE TAGRISSO® DELIVERED



AN UNPRECEDENTED

18.9 vs 10.2

months median PFS vs erlotinib/gefitinib in the FLAURA study

Hazard ratio=0.46 (95% CI: 0.37, 0.57), *P*<0.0001

Randomized, double-blind, active-controlled trial in 556 patients with metastatic EGFRm NSCLC who had not received prior systemic treatment for advanced disease. Patients were randomized 1:1 to either TAGRISSO (n=279; 80 mg orally, once daily) or EGFR TKI comparator (n=277; gefitinib 250 mg or erlotinib 150 mg, once daily). Crossover was allowed for patients in the EGFR TKI comparator arm at confirmed progression if positive for the EGFR T790M resistance mutation. Patients with CNS metastases not requiring steroids and with stable neurologic status were included in the study. The primary endpoint of the study was PFS based on investigator assessment (according to RECIST v.1.1). Secondary endpoints included OS, ORR, and DOR.[1,2]

INDICATION

TAGRISSO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

SELECT SAFETY INFORMATION

- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed
- Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSO-treated patients. Of the 1142 TAGRISSO-treated patients in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec. No QTc-related arrhythmias were reported.

AstraZeneca

GROUNDBREAKING EFFICACY

DOSING

First-line TAGRISSO offers convenient, once-daily dosing, with or without food[1]

ALL SUBGROUPS

Delivered consistent PFS results across all subgroups, including patients with or without CNS metastases[2]

NCCN CATEGORY 1 RECOMMENDED

First-line osimertinib (TAGRISSO) is a National Comprehensive Cancer Network® (NCCN®) Category 1* option[3]

*Category 1 means NCCN has uniform consensus based upon high-level evidence.[3]

SELECT SAFETY INFORMATION

- Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia
- Cardiomyopathy occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10% from baseline and to <50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO
- Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist
- Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose
- Most common adverse reactions (≥20%) were diarrhea, rash, dry skin, nail toxicity, stomatitis, fatigue and decreased appetite

Abbreviations: CNS, central nervous system; DOR, duration of response; EGFRm, epidermal growth factor receptor mutation-positive; NSCLC, non-small cell lung cancer; ORR, overall response rates; OS, Overall Survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TKI, tyrosine kinase inhibitor.

REFERENCES: 1. TAGRISSO [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018. **2.** Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378(2):113-125. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC V.5.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed June 29, 2018. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. To view the most recent and complete version of the guideline, go online to NCCN.org.

Please see Brief Summary of Prescribing Information on adjacent pages.

LEARN MORE AT TagrissoHCP.com

TAGRISSO®
osimertinib

TAGRISSO® (osimertinib) tablets, for oral use

Brief Summary of Prescribing Information.
For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

First-line Treatment of EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

TAGRISSO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

Patient Selection

Select patients for the first-line treatment of metastatic EGFR-positive NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor or plasma specimens *[see Clinical Studies (14) in the full Prescribing Information]*. If these mutations are not detected in a plasma specimen, test tumor tissue if feasible.

Information on FDA-approved tests for the detection of EGFR mutations is available at http://www.fda.gov/companiondiagnostics.

Recommended Dosage Regimen

The recommended dosage of TAGRISSO is 80 mg tablet once a day until disease progression or unacceptable toxicity. TAGRISSO can be taken with or without food.

If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

Administration to Patients Who Have Difficulty Swallowing Solids

Disperse tablet in 60 mL (2 ounces) of non-carbonated water only. Stir until tablet is dispersed into small pieces (the tablet will not completely dissolve) and swallow immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 mL to 240 mL (4 to 8 ounces) of water and immediately drink.

If administration via nasogastric tube is required, disperse the tablet as above in 15 mL of non-carbonated water, and then use an additional 15 mL of water to transfer any residues to the syringe. The resulting 30 mL liquid should be administered as per the nasogastric tube instructions with appropriate water flushes (approximately 30 mL).

Dosage Modifications

Adverse Reactions

Table 1. Recommended Dosage Modifications for TAGRISSO

Target Organ	Adverse Reaction[a]	Dosage Modification
Pulmonary	Interstitial lung disease (ILD)/Pneumonitis	Permanently discontinue TAGRISSO.
Cardiac	QTc† interval greater than 500 msec on at least 2 separate ECGs[b]	Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then resume at 40 mg dose.
	QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	Permanently discontinue TAGRISSO.
	Symptomatic congestive heart failure	Permanently discontinue TAGRISSO.
Other	Adverse reaction of Grade 3 or greater severity	Withhold TAGRISSO for up to 3 weeks.
	If improvement to Grade 0-2 within 3 weeks	Resume at 80 mg or 40 mg daily.
	If no improvement within 3 weeks	Permanently discontinue TAGRISSO.

[a] Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0).
[b] ECGs = Electrocardiograms
† QTc = QT interval corrected for heart rate

Drug Interactions

Strong CYP3A4 Inducers

If concurrent use is unavoidable, increase TAGRISSO dosage to 160 mg daily when co-administering with a strong CYP3A inducer. Resume TAGRISSO at 80 mg 3 weeks after discontinuation of the strong CYP3A4 inducer *[see Drug Interactions (7) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal.

Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed *[see Dosage and Administration (2.4) and Adverse Reactions (6) in the full Prescribing Information]*.

QTc Interval Prolongation

Heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 1142 patients treated with TAGRISSO in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. No QTc-related arrhythmias were reported.

Clinical trials of TAGRISSO did not enroll patients with baseline QTc of > 470 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

Cardiomyopathy

Across clinical trials, cardiomyopathy (defined as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary edema or decreased ejection fraction) occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal.

A decline in left ventricular ejection fraction (LVEF) ≥ 10% from baseline and to less than 50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment.

Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

Keratitis

Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist.

Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, osimertinib caused post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the recommended clinical dose. When males were treated prior to mating with untreated females, there was an increase in preimplantation embryonic loss at plasma exposures of approximately 0.5 times those observed at the recommended dose of 80 mg once daily. Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose *[see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

QTc Interval Prolongation *[see Warnings and Precautions (5.2) in the full Prescribing Information]*

Cardiomyopathy *[see Warnings and Precautions (5.3) in the full Prescribing Information]*

Keratitis *[see Warnings and Precautions (5.4) in the full Prescribing Information]*

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 section reflect exposure to TAGRISSO in 1142 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)], two single arm trials [AURA Extension (n=201) and AURA2 (n=210)], and one dose-finding study, AURA1 (n=173) *[see Warnings and Precautions (5) in the full Prescribing Information]*.

The data described below reflect exposure to TAGRISSO (80 mg daily) in 558 patients with EGFR mutation-positive, metastatic NSCLC in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)]. Patients with a history of interstitial lung disease, drug induced interstitial disease or radiation pneumonitis that required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from enrollment in these studies.

Previously Untreated EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer

The safety of TAGRISSO was evaluated in FLAURA, a multicenter international double-blind randomized (1:1) active controlled trial conducted in 556 patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, unresectable or metastatic NSCLC who had not received previous systemic treatment for advanced disease. The median duration of exposure to TAGRISSO was 16.2 months.

The most common adverse reactions (≥20%) in patients treated with TAGRISSO were diarrhea (58%), rash (58%), dry skin (36%), nail toxicity (35%), stomatitis (29%), and decreased appetite (20%). Serious adverse reactions were reported in 4% of patients treated with TAGRISSO; the most common serious adverse reactions (≥1%) were pneumonia (2.9%), ILD/pneumonitis (2.1%), and pulmonary embolism (1.8%). Dose reductions occurred in 2.9% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (4.3%), diarrhea (2.5%), and lymphopenia (1.1%). Adverse reactions leading to permanent discontinuation occurred in 13% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3.9%).

Tables 2 and 3 summarize common adverse reactions and laboratory abnormalities which occurred in FLAURA. FLAURA was not designed to demonstrate a statistically significant reduction in adverse reaction rates for TAGRISSO, or for the control arm, for any adverse reaction listed in Tables 2 and 3.

Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA*

Adverse Reaction	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
	Any Grade (%)	Grade 3 or higher (%)	Any Grade (%)	Grade 3 or higher (%)
Gastrointestinal Disorders				
Diarrhea[a]	58	2.2	57	2.5
Stomatitis	29	0.7	20	0.4
Nausea	14	0	19	0
Constipation	15	0	13	0
Vomiting	11	0	11	1.4
Skin Disorders				
Rash[b]	58	1.1	78	6.9
Dry skin[c]	36	0.4	36	1.1
Nail toxicity[d]	35	0.4	33	0.7
Pruritus[e]	17	0.4	17	0
Metabolism and Nutrition Disorders				
Decreased appetite	20	2.5	19	1.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough	17	0	15	0.4
Dyspnea	13	0.4	7	1.4
Neurologic Disorders				
Headache	12	0.4	7	0
Cardiac Disorders				
Prolonged QT Interval[f]	10	2.2	4	0.7
General Disorders and Administration Site Conditions				
Fatigue[g]	21	1.4	15	1.4
Pyrexia	10	0	4	0.4
Infection and Infestation Disorders				
Upper Respiratory Tract Infection	10	0	7	0

* NCI CTCAE v4.0
[a] One grade 5 (fatal) event was reported (diarrhea) for EGFR TKI comparator
[b] Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, rash follicular, erythema, folliculitis, acne, dermatitis, dermatitis acneiform, drug eruption, skin erosion.
[c] Includes dry skin, skin fissures, xerosis, eczema, xeroderma.
[d] Includes nail bed disorder, nail bed inflammation, nail bed infection, nail discoloration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.
[e] Includes pruritus, pruritus generalized, eyelid pruritus.
[f] The frequency of "Prolonged QT Interval" represents reported adverse events in the FLAURA study. Frequencies of QTc intervals of >500 ms or >60 ms are presented in Section 5.2.
[g] Includes fatigue, asthenia.

Table 3. Laboratory Abnormalities Worsening from Baseline in ≥ 20% of Patients in FLAURA

Laboratory Abnormality[a,b]	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4 (%)	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4 (%)
Hematology				
Lymphopenia	63	5.6	36	4.2
Anemia	59	0.7	47	0.4
Thrombocytopenia	51	0.7	12	0.4
Neutropenia	41	3.0	10	0
Chemistry				
Hyperglycemia[c]	37	0	31	0.5
Hypermagnesemia	30	0.7	11	0.4
Hyponatremia	26	1.1	27	1.5
Increased AST	22	1.1	43	4.1
Increased ALT	21	0.7	52	8
Hypokalemia	16	0.4	22	1.1
Hyperbilirubinemia	14	0	29	1.1

[a] NCI CTCAE v4.0
[b] Each test incidence, except for hyperglycemia, is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (TAGRISSO range: 267 - 273 and EGFR TKI comparator range: 256 - 268)
[c] Hyperglycemia is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TAGRISSO (179) and EGFR comparator (191)

DRUG INTERACTIONS

Effect of Other Drugs on Osimertinib

Strong CYP3A Inducers

Co-administering TAGRISSO with a strong CYP3A4 inducer decreased the exposure of osimertinib compared to administering TAGRISSO alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Decreased osimertinib exposure may lead to reduced efficacy.

Avoid co-administering TAGRISSO with strong CYP3A inducers. Increase the TAGRISSO dosage when co-administering with a strong CYP3A4 inducer if concurrent use is unavoidable *[see Dosage and Administration (2.4) in the full Prescribing Information]*. No dose adjustments are required when TAGRISSO is used with moderate and/or weak CYP3A inducers.

Effect of Osimertinib on Other Drugs

Co-administering TAGRISSO with a breast cancer resistant protein (BCRP) or P-glycoprotein (P-gp) substrate increased the exposure of the substrate compared to administering it alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Increased BCRP or P-gp substrate exposure may increase the risk of exposure-related toxicity.

Monitor for adverse reactions of the BCRP or P-gp substrate, unless otherwise instructed in its approved labeling, when co-administered with TAGRISSO.

Drugs That Prolong the QTc Interval

The effect of co-administering medicinal products known to prolong the QTc interval with TAGRISSO is unknown. When feasible, avoid concomitant administration of drugs known to prolong the QTc interval with known risk of Torsades de pointes. If not feasible to avoid concomitant administration of such drugs, conduct periodic ECG monitoring *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1) in the full Prescribing Information]*, TAGRISSO can cause fetal harm when administered to a pregnant woman. There are no available data on TAGRISSO use in pregnant women. Administration of osimertinib to pregnant rats was associated with embryolethality and reduced fetal growth at plasma exposures 1.5 times the exposure at the recommended clinical dose *(see Data)*. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

When administered to pregnant rats prior to embryonic implantation through the end of organogenesis (gestation days 2-20) at a dose of 20 mg/kg/day, which produced plasma exposures of approximately 1.5 times the clinical exposure, osimertinib caused post-implantation loss and early embryonic death. When administered to pregnant rats from implantation through the closure of the hard palate (gestation days 6 to 16) at doses of 1 mg/kg/day and above (0.1 times the AUC observed at the recommended clinical dose of 80 mg once daily), an equivocal increase in the rate of fetal malformations and variations was observed in treated litters relative to those of concurrent controls. When administered to pregnant dams at doses of 30 mg/kg/day during organogenesis through lactation Day 6, osimertinib caused an increase in total litter loss and postnatal death. At a dose of 20 mg/kg/day, osimertinib administration during the same period resulted in increased postnatal death as well as a slight reduction in mean pup weight at birth that increased in magnitude between lactation days 4 and 6.

Lactation

Risk Summary

There are no data on the presence of osimertinib or its active metabolites in human milk, the effects of osimertinib on the breastfed infant or on milk production. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise women not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating TAGRISSO.

Contraception

TAGRISSO can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of TAGRISSO *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

Infertility

Based on animal studies, TAGRISSO may impair fertility in females and males of reproductive potential. The effects on female fertility showed a trend toward reversibility. It is not known whether the effects on male fertility are reversible *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

Pediatric Use

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

Geriatric Use

Forty-three percent (43%) of the 1142 patients in FLAURA (n=279), AURA3 (n=279), AURA Extension (n=201), AURA2 (n=210), and AURA1, (n=173) were 65 years of age and older. No overall differences in effectiveness were observed based on age. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (13.4% versus 9.3%) and more frequent dose modifications for adverse reactions (13.4% versus 7.6%) in patients 65 years or older as compared to those younger than 65 years.

Renal Impairment

No dose adjustment is recommended in patients with creatinine clearance (CLcr) 15 - 89 mL/min, as estimated by Cockcroft-Gault. There is no recommended dose of TAGRISSO for patients with end-stage renal disease (CLcr < 15 mL/min) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Hepatic Impairment

No dose adjustment is recommended in patients with mild to moderate hepatic impairment (Child-Pugh A and B or total bilirubin ≤ ULN and AST > ULN or total bilirubin 1 to 3 times ULN and any AST). There is no recommended dose for TAGRISSO for patients with severe hepatic impairment (total bilirubin between 3 to 10 times ULN and any AST) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

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FROM THE EDITOR-IN-CHIEF


ALVARNAS

Oncology in the Time of "Moore's Law"

IN AN ARTICLE PUBLISHED in *Electronics Magazine* on April 9, 1965, Intel cofounder Gordon Earle Moore noted that the number of transistors in an integrated circuit doubled every year.[1] He extrapolated that this rate of growth in computing power would continue to double every 2 years throughout the late 1960s and in to the 1970s and 1980s. The prediction, which became known as Moore's Law, proved prescient. Intel and other industry leaders took this as both a prediction for the pace of innovation and a push for the industry to create "computing [that] would dramatically increase in power, and decrease in relative cost, at an exponential pace."[2] From 1965 to today, the technologies, depth of innovation, and corresponding impact from discoveries made in the pursuit of achieving and sustaining Moore's vision have affected our lives in profound and unexpected days. Conversations rarely take place today without someone glancing at a smartphone to close a business deal, to let family know they will be late, or to post pictures of the conversation on a social media site.

Oncology is now in the midst of realizing its own Moore's Law. Some speculate that data generated in oncology are doubling at a rate of every 3.5 years. A recent IQVIA report noted, "Over the past 5 years, 61 cancer drugs, each approved in 1 or more tumors, have impacted the treatment of 23 different cancer types."[3] This level of innovation has translated into an enormous human impact. The American Cancer Society found that over the past 25 years, the cancer death rate has declined by 27% and that this decline "translates to about 1.5% per year and more than 2.6 million deaths avoided between 1991 and 2016."[4] Numerous industry leaders are positioning themselves for a big data revolution in oncology in which the almost unfathomable amount of data compiled from the growing field of genomic testing can be integrated with discreet patient data and innovative therapeutics to bring better care faster to patients affected by cancer.[5]

Inasmuch as new data in oncology are translating into a wealth of new information that may be leveraged to deliver far more effective treatments to patients affected by cancer, new and significant challenges are popping up in this time of extraordinary innovation. Unlike the marked relative decline in the costs of integrated chip-based devices, costs in new and innovative cancer treatments have grown dramatically. The IQVIA report notes[3]:

Spending on cancer drugs in the United States has doubled since 2012 and reached almost $50 billion in 2017, with two-thirds of the growth tied to use of drugs launched within the past 5 years. . . .

Spending on cancer medicines is heavily concentrated, with the top 35 drugs accounting for 80% of total spending.[3]

Moreover, although oncology drug costs are growing at a rapid—some would say an unsustainable—pace there are additional challenges to the oncology delivery system based on issues of patient access to care, provider knowledge gaps, and the challenges related to the still-unresolved question of how to more effectively manage social determinants of health.

Some of the goals of *Evidence-Based Oncology*™ are to disseminate information regarding key innovations in oncology care while also working to engage key stakeholder thought leaders in conversations geared at translating the extraordinary innovations of "oncology in the time of Moore's Law" into a clinically effective, equitably available, and financially sustainable system of care delivery.

In this month's issue, we have the opportunity to learn about advancing care technologies and discuss some of the financial and practical challenges of sustainably delivering these innovations. These include clinical updates from the National Comprehensive Cancer Network (NCCN) on ovarian and prostate cancers and shining a spotlight on the growing importance of immunotherapy in the care of patients with non–small cell lung cancer. Sanjeet Dadwal, MD, from City of Hope, in Duarte, California, summarizes what is new in supporting and managing patients with febrile neutropenia. The challenges and opportunities of delivering new care technologies at a sustainable price point are explored in discussions from NCCN on biosimilars, end-of-life care, and survivorship. We also explore the great opportunities and enormous financial challenges of delivering chimeric antigen receptor T-cell therapeutics in panel discussion.

There have never been greater opportunities for patients to survive heretofore ineffectively treated cancers. The growing development of targeted therapeutics and the rapidly expanding domain of immune-oncology portend even greater abilities to serve patients with historically unmet cancer care needs. We have the ability to move forward into this new era of knowledge, with greater opportunity for cures, more equitable and navigable systems of care, and sustainable costs. ◆

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PATEL

Evidence-Based Oncology™ Welcomes Kashyap Patel, MD, as Associate Editor

Kashyap Patel, MD, ABOIM, BCMAS, the president of Carolina Blood and Cancer Care Associates (CBCCA), based in Rock Hill, South Carolina, has joined the editorial team of *Evidence-Based Oncology*™ (*EBO*) as associate editor. Patel has been a frequent contributor to *EBO* and a participant in the Institute for Value-Based Medicine series. He is practicing medical oncologist and is board-certified in hematology, oncology, and internal medicine, having completed his residency at Jamaica Hospital in New York City and his fellowship in hematology and medical oncology at Thomas Jefferson University Hospital in Philadelphia.

Patel is the current vice president of the Community Oncology Alliance and serves on the group's Oncology Payment Reform and Biosimilars committees; he is a trustee and chairman for clinical affairs for the Association of Community Cancer Centers. He is a nationally recognized expert on biosimilars, precision medicine, and implementation of principles of value-based care. He serves on committees for the American Society of Clinical Oncology, the National Committee on Quality Assurance, and is a longtime adviser of the MolDx division of Palmetto GBA. Patel and the team at CBCCA have successfully pursued payment reform under CMS' Oncology Care Model, and in this issue he and his co-authors share the second part of a series on that process. ◆

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FROM THE CHAIRMAN

Putting Evidence Into the CAR T-cell Reimbursement Equation

FOR NEARLY A YEAR, cancer centers that administer the breakthrough treatment, chimeric antigen receptor (CAR) T-cell therapy, have been trapped in a reimbursement twilight zone: CMS backed away from a value-based agreement reached with Novartis, the manufacturer of the therapy, but did not set a replacement, thus leaving payment decisions to the regional Medicare Administrative Contractors (MACs). Given the cost of CAR T-cell therapy, either $373,000 or $495,000 just to manufacture the treatment, the vacuum created when CMS canceled the Novartis arrangement meant that cancer centers were losing money on every Medicare patient they treated. There were fears in some states that Medicaid patients with acute lymphoblastic lymphoma who might be saved by CAR T would be unable to access it.

As we learned during a lively panel discussion at the March meeting of the National Comprehensive Cancer Network (NCCN), covered on **SP178**, this situation was not sustainable. And after a year spent gathering input during a National Coverage Analysis, CMS issued its proposed reimbursement plan: Coverage With Evidence Development. Under this model, patients who receive CAR T-cell therapy covered with public funds must be enrolled in clinical trials or registries and tracked for at least 2 years. In Medicare especially, there is a need to develop evidence for patients largely left out of clinical trials that led to CAR T-cell therapy approvals. Some experts say these data are needed, and the proposal makes sense. But others, including our editor-in-chief, Joseph Alvarnas, MD, of City of Hope in Duarte, California, warn that the CMS proposal as constructed could burden cancer centers—so much so that many will decide they cannot afford to administer the treatment. Access to treatment, already a challenge for those who must travel from remote locations, could get worse before it gets better. And there's the concern that the language of the proposal itself, with repeat references to the word "hospital," may exclude community oncology centers that are already taking part in clinical trials.

Biotechnology advocates had other issues with the CMS plan as written. Would it limit the inclusion of new CAR T-cell indications? Would it block clinicians from using this treatment earlier in the course of care, as has been discussed at scientific meetings? Would patients have the right to opt out of being in a registry or a study? During the NCCN panel discussion, Jennifer Malin, MD, PhD, senior medical director for oncology and genetics at United Healthcare, suggested that the pharmaceutical companies that manufacture CAR T-cell therapy must cover the cost of gathering evidence. That seemed to be news to some oncologists in the room.

The observation that pharma will help gather the data if it's in their interest speaks to a larger point: The current process will create a framework to pay for the coming wave of very expensive gene therapies that do more than add years to life—they potentially cure disease. Getting this right is in everyone's interest, not just CMS. And it may likely require models that will take years to develop. In the meantime, some patients must be saved today. ◆

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

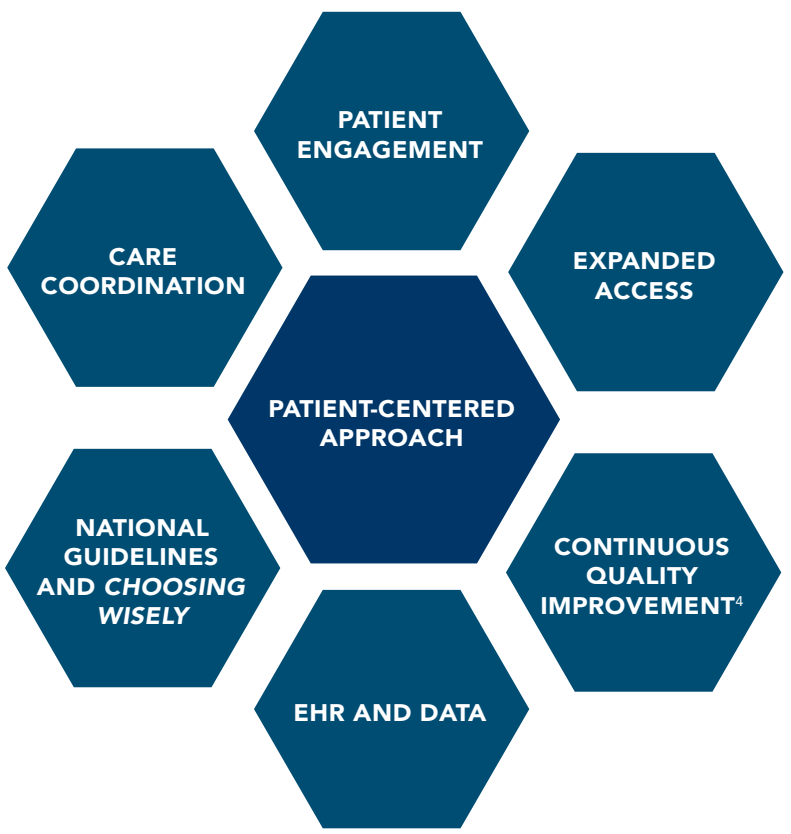
Road Map to Success in the OCM: From Team Building to Implementation

Kashyap Patel, MD, ABOIM, BCMAS; Maharshi Patel, MBA; Taylor Lavender, BS, PA; Dhwani Mehta, MS, RD; Sashi Naidu, MD; and Asutosh Gor, MD

IN THE PREVIOUS ARTICLE, "Road map to Success in the Oncology Care Model: Tapping into Human Potential via Sustained Engagement,"[1] we discussed team-building exercises that allowed members of our practice, Carolina Blood and Cancer Care Associates, to evaluate and tap into our biggest strength: the unused potential of our employees, given their experience. We also talked about how we recognized the problems with our previous model that stemmed from siloed, fragmented care and found ways to address them with our collective wisdom, ultimately leading to a roadmap toward patient-centered cancer care (PCCC). We combined subjective human experiences with an objective checklist that allowed us to remain in compliance with our road map. These exercises allowed us to dive deep into the human psyche and design truly patient-centric solutions. We learned that a true patient-centered approach would be a combination of objective, numerical, centripetal measures defined in the Oncology Care Model (OCM) and subjective centrifugal emotions, aspirations, and expectations. We created smart teams, enabling an efficient transition from volume to value. These exercises were similar to building a higher pyramid on top of what we already achieved during our journey toward Patient-Centered Speciality Practice (PCSP) accreditation by the the National Committee for Quality Assurance (NCQA)[2] in 2015. Although the transition to being a PCSP was speciality agnostic and truly patient centric, the OCM gave us a blueprint that was specific to the needs of PCCC.

Our team saw what was on the horizon in the early part of this decade, as the buzzword "value-based care" became common. We started planning to change proactively rather than reactively. Our leadership started engaging with payers to develop an active partnership to make the transition to value. We reached out to HHS as well as our largest commercial payer, BlueCross BlueShield of South Carolina (BCBSSC) to learn their vision and goals for better care. After a series of meetings, we narrowed down our transformation process to meet PCSP accreditation by NCQA (**Figure 1**). All these activities happened in parallel to us applying for OCM status.[3]

Figure 1. PCSP Transition Preparations



EHR indicates electronic health record; PCSP, patient-centered specialty practice.
[4]Continuous Quality Improvement is an accreditation of the Commission on Cancer.

PCCC Transition Leading to PCSP Recognition

The process was divided into 6 core areas (Figure 1), with an overall aim to improve coordinated care and to fulfill the requirements of the PCSP accreditation, which led to our recognition as the first oncology clinic in South Carolina to achieve this status. We felt that PCSP accreditation helped us to improve the quality of patient care, reduce unnecessary costs driven by avoidable factors, and put the practice on the path to becoming a patient-centric experience. As a part of this last goal, our cancer clinic and infusion services already had a foundation corresponding with many of the OCM's practice requirements. These changes aligned with our philosophy of including population health management strategies to optimize clinical effectiveness and efficiency. Patient engagement helped us achieve shared decision making and for patients and care givers to become more proactive. In order to standardize treatment offerings, we adopted *Choosing Wisely* recommendations from specialty societies. These initial steps taken from 2014 to 2015 helped us prime our practice to be ready for the OCM. Upon being selected for the OCM, we still had to modify our practice to fulfill standards to remain in compliance with standards; therefore, we started additional learning systems. However, the OCM had required prescriptive standards we also had to meet to remain in compliance. Therefore, we made additional preparations and took steps to shift from a specialty-agnostic PCSP to OCM through a transition into PCCC.

Steps to Transition to OCM Learning From Sustained Engagement

As we mentioned in the previous article, we brought our employees on board with the OCM transformation. In addition to the sustained engagement (SE) workshop that we discussed in the February issue of *Evidence-Based Oncology*™,[1] we carried out a series of meetings, initially on a weekly basis before shifting to monthly, to come up with ideas for a smooth transition to meet OCM requirements. Although the focus of these activities was on developing team spirit, we were also looking for group input into adhering to prescriptive steps, including 13-point care plans from the Institute of Medicine[5] (IOM), now the National Academy of Medicine, navigation, etc. Being a small independent practice with resource constraints, we sought to crosstrain our employees within the scope of their existing work and licenses (**Figure 2**). We added nursing and pharmacy staff and encouraged all employees to undergo certification in oncology navigation. We also designated a lead employee to be the financial navigator, with the sole function of providing and coordinating resource lists for all patients who were either uninsured or underinsured.

Figure 2. Onboarding Employees

OCM indicates Oncology Care Model; SE, sustained engagement.

Figure 3. Clinical Care Components: OCM and PCCC Transition

NCCN indicates National Comprehensive Cancer Network; OCM, Oncology Care Model; PCCC, patient-centered cancer care.

PCCC Transition Focusing on Clinical Care

At the conclusion of the SE workshop, we concluded that additional steps would be necessary to enhance care through OCM requirements. At the end of the retreat, our team came up with several suggestions to highlight 2 areas of additional practice transformation.

The first one focused on addressing areas specific to improving clinical care (**Figure 3**) and the second focused on nonclinical pathways to address financial and other hardships experienced by patients and caregivers. Recognizing that financial toxicities are some of the most common but frequently ignored factors adversely affecting prognosis, we created lists of priorities and ways to address them.

A majority of the OCM participants had difficulties in implementing the 13-point IOM care plan,[5] which involved multiple dimensions of communication, care coordination, etc. During our SE retreats, our employees came up with idea of designing a comprehensive patient education booklet, which addressed common elements such as employee job descriptions, adverse effects of chemotherapy, etc. Ultimately, we compiled a booklet covering most aspects of an IOM care plan. We kept additional folders to individualize material for each patient.

We also made significant financial and technological investments in starting in-house diagnostics, including flow cytometry and high-resolution computerized tomography scanning to address common emergencies for our patients. We added pharmacy staff to start in-office dispensing under the MD license to have better control over dispensing expensive oral chemotherapeutic agents. We added full-time nutrition and smoking-cessation counselors for lifestyle modification for secondary prevention. We also started clinical trials. Additionally, we decided to adopt evidence blocks from the National Comprehensive Cancer Network to use comparatively efficacious but cost-effective therapies.[6]

We had already started providing expanded access, including same-day, walk-in, and weekend access, as well as on an as-needed basis as a part of NCQA accreditation. After reviewing the feedback report from the CMMI at the beginning of the pilot program, we saw opportunities to reduce emergency department visits and hospital admissions as low-hanging fruit. However, we did not have resources to provide after-hours coverage to treat non-life-threatening emergencies. We collaborated with a local urgent care center to provide care, including labs, diagnostic radiological services, and infusion services. We essentially were able to provide all noncritical care in an outpatient setting.

One of our physicians was already certified in hospice and palliative care, and he also underwent certificate training as a voluntary chaplain. What we started as specialty-agnostic patient-centered care with a PCSP came full circle as a clinical care continuum specifically covering oncology care.

The second aspect of oncology-specific transformation we underwent included identifying nonclinical challenges patients face. These challenges include daily transport, financial hardships, and limited coverage.

Our team first listed all such challenges[1] and created a resource list. We learned that our local utility companies had a program that waived utility bills for patients with limited life expectancy. We made a list of volunteers willing to transport patients for treatment. We also partnered with a local nonprofit agency aging (Catawba Agency on Aging) to facilitate resource lists and assist patients to qualify for dual-eligibility status (Medicare and Medicaid) and for federal low-income subsidy programs through Medicare Part D, which would provide oral drug coverage to dual-eligible citizens.[7] We included all this information in our patient education booklets.

What started as baby steps to transition our practice from volume to value via PCSP accreditation resulted in a very efficient and truly PCCC delivery site recognized by NCQA and CMMI. We additionally started an OCM pilot with BCBSSC.

The practice transformation process took time and resources. It often seemed unachievable, but after completing the transformation to a PCSP, we have been able to negotiate reimbursement for additional nonevaluation and management cognitive services as well as for weekend services.

Pursuit of the practice transformation had already started reflecting with better care for our patients and yielded many benefits to all the stakeholders for our group. Patients experienced the benefits of fully patient-centric care, greater care coordination and communication, a more well-established relationship with their physicians, and real-time/on-demand access to care. Our physicians experienced the benefits of standardization of the science of medicine, practice revenue stabilization, improved efficiency, and standardized data compilation.

Payers benefited from a reduction in "cancer spend" and increased patient engagement in the care process, care that is assured to be appropriate to the patient's condition, and focus on reducing avoidable complications.

We currently operate 2 infusion suites. Both facilities are single-story buildings allowing patients easy access around the entire facility. Aesthetic appeal was a large priority when creating the buildings to ensure a warm and welcoming environment for the patients, with the Rock Hill infusion suite facing patients toward a large glass wall that overlooks a beautiful healing garden featuring palm trees, a large gazebo, and fountain, and the Lancaster suite complete with a glass-domed sunroof ceiling, an indoor fountain, and a large indoor garden. The traits of both offices helped improve the patient experience by diverting their attention from their discomfort and illness.

Next: We will share the results of our transformation to the OCM. ◆

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FDA Expands Patient Inclusion Criteria for Cancer Clinical Trials

Samantha DiGrande

IN MARCH, the FDA published 4 draft guidances and 1 final guidance in an effort to broaden patient participation in cancer clinical trials and to promote the inclusion of pediatric patients and patients with comorbidities that can occur alongside cancer. These efforts are also to increase patient accrual, broaden patients' access to clinical trials, and lead to trial results that better represent treatment effects in the real world.

"When drug developers design a clinical trial, they identify eligibility criteria to define what types of patients qualify for participation in the trial. They base the eligibility criteria on factors such as the mechanism of action of the drug, characteristics of the disease, the expected toxicities of the investigational drug, and the ability to recruit trial participants from the patient population to meet the objectives of the clinical trial," said then-FDA Commissioner Scott Gottlieb, MD, in a statement.[1]


GOTTLIEB

"However, in trials testing treatments for cancer, some eligibility criteria have become commonly accepted over time or used as a template across trials without a clear scientific or clinical rationale or justification. In other cases, eligibility criteria can be deliberately restrictive, even though it is not clinically merited. As a result, cancer patients are often unnecessarily restricted from participating in trials."

Minimum Age for Pediatric Patients

The first guidance, "Cancer Clinical Trial Eligibility Criteria: Minimum Age for Pediatric Patients—Guidance for Industry,"[2] discussed minimum age eligibility criteria for pediatric patients in cancer clinical trials. The guidance also addressed specific situations in which the inclusion of pediatric patients may be appropriate based on "disease biology and clinical course, molecular target of the investigational drug, and/or its molecular mechanism."

Traditionally, pediatric patients have not been included in adult clinical trials, which generally specify that a patient must be 18 years or older to be included. Typically, pediatric trials of the same drug have been initiated after 1 or more adult clinical trials have been completed, or after the drug or treatment has received initial FDA approval for adults. This has "delayed the development of and access to potentially effective new cancer drugs for the pediatric population," according to the guidance. This guidance makes recommendations for the inclusion of pediatric populations, including both children, aged 2 to 11 years, and adolescents, aged 11 to 17 years.

Patients With HIV, Hepatitis B Virus, or Hepatitis C Virus Infections

The next guidance[3] provided recommendations for the inclusion of patients with cancer who also have HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV) infections. Historically, patients with cancer who have such comorbidities are often excluded from clinical trials despite the fact that HIV and HBV infections can be chronically managed, and HCV can be cured with antiviral therapy. "Expanding cancer clinical trial eligibility to be more inclusive of patients with HIV, HBV, or HCV infections is justified in many cases, and may accelerate the development of effective therapies in cancer patients with these chronic infections," read the guidance.

FDA recommendations include considering clinical trial eligibility based on CD4+ T cell counts, history of AIDS-defining opportunistic infections, and exclusion of specific antiretroviral therapy drugs, among others.

Patients With Organ Dysfunction or Prior or Concurrent Malignancies

The FDA noted[4] that patients with organ dysfunction are often excluded from clinical trials, "regardless of knowledge of the metabolic pathways and excretory routes of the investigational drug." Due to the increasing lifespan of the general population, the number of patients with comorbid renal disease, cardiac disease, and hepatic dysfunction is also increasing. By excluding patients from cancer clinical trials who also have organ dysfunction, trial recruitment inherently favors younger patients, which may not fully represent the population that the drug will be indicated to treat.

The FDA recommended that for patients with organ dysfunction, where pharmacokinetics and major routes of elimination are not well understood, "it is reasonable to enroll only patients with relatively preserved organ function (primarily renal and hepatic) in cancer clinical trials. As data on toxicity including preclinical and clinical toxicity, [pharmacokinetics], and/or pharmacodynamics become available during drug development, protocols should be revised to include patients with compromised organ function where safe parameters regarding dosage adjustments have been determined," read the guidance.

> **"A clinical trial that's more representative of the patient population can maximize the generalizability of the trial results and the ability to understand the therapy's benefit–risk profile across the patient population likely to receive the drug in clinical practice."**
>
> —Scott Gottlieb, MD, then-FDA commissioner

Brain Metastases

In this draft guidance,[5] the FDA explained that patients with brain metastases have historically been excluded from clinical trials due to concerns of poor functional status, shortened life expectancy, or increased risk of toxicity.

Each year, an estimated 70,000 patients living with cancer in the United States are diagnosed with brain metastases. Certain malignancies, such as melanoma, lung cancer, and breast cancer, have shown an increasing incidence of brain metastases. The FDA wrote that "patients with cancers that commonly metastasize to the brain (eg, lung cancer, breast cancer, melanoma) should be included in early drug development trials, either in separate cohorts or in cohorts with planned subset analyses to assess preliminary efficacy and toxicity in patients with brain metastases."

Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials

The final guidance document[6] delivered within this package focused on the inclusion of pediatric patients who have cancers similar in histology and biologic behavior to those found in adults. The FDA offered guidelines around the inclusion of adolescent patients after some initial adult pharmacokinetic and toxicity data are obtained. Additionally, in terms of dose escalation, for drugs with body size–adjusted dosing for adults, "adolescent patients should receive the same body size–adjusted dose (mg/kg or mg/m^2) that is administered in adults. Safety monitoring data in such a trial should also be examined for any age-related differences."

On the release of the package of guidance documents, Gottlieb said, "The FDA issued new recommendations for broadening cancer trial eligibility criteria that are designed to help address these challenges. A clinical trial that's more representative of the patient population can maximize the generalizability of the trial results and the ability to understand the therapy's benefit–risk profile across the patient population likely to receive the drug in clinical practice." ◆

continued ▸

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Not Just the "Soft Stuff": How Data Deployment, Artificial Intelligence Can Restore Relationships in Oncology Care

Mary Caffrey

PAGE

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COX

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THE REVOLUTION IN CANCER CARE isn't just about the wave of life-saving therapies or the role of genetics in pinpointing exactly who should get which drug and when. As Ray D. Page, DO, PhD, FACOI, tells it, change also means getting back to the basics so that the relationship between doctor and patient drives care—not insurance companies or Medicare or rules from the FDA.

Giving patients what they need at a fair price, not care they don't need or can't afford, is how Page envisions transformation. The president and director of research at The Center for Cancer and Blood Disorders (CCBD), in Fort Worth, Texas, has plenty to say about the barriers that are preventing shared decision making—from the bureaucracy of Obamacare to the failed promise of electronic health records (EHRs), which he called, "the number one cause of physician dissatisfaction."[1]

Connecting payment to quality, which includes not just outcomes but what Page calls "the art of medicine," is a tall order. And in oncology care, he said, there's a long way to go. Finding better tools to restore the doctor–patient relationship was on Page's mind March 7, 2019, as he moderated a meeting of the Institute for Value-Based Medicine in Oncology, an initiative of *The American Journal of Managed Care*®. The session at the Four Seasons, Las Colinas, in Irving, Texas, which featured presentations and discussion from John Cox, DO, MBA, FASCO, professor of medicine, University of Texas (UT) Southwestern; Kashyap Patel, MD, ABOIM, BCMAS, president, Carolina Blood and Cancer Care Associates; Barry Russo, chief executive officer, CCBD; and Tony Willoughby, PharmD, president, Pharmacy Solutions, StratiFi Health.

"You should be able to negotiate a rate for services at a fair market value price," Page said, as he discussed his challenges with the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA),[2] which sought to shift healthcare away from fee-for-service (FFS) toward payment based on quality.

But Page said much of MACRA has made things more complex for oncology practices. Given the choice between the Merit-based Incentive Payment System and an alternative payment model (APM), Page's practice pursued the Oncology Care Model (OCM), an APM regulated by the Center for Medicare and Medicaid Innovation (CMMI).[3] "The complexity was just unbelievable," he said.

CMMI hasn't been able to answer all of Page's questions on how the model works or how practices are rewarded for quality. A big challenge—not just for Page's practice but for many others—is the inability to control which patients come through the front door or what types of cancer they have, which drives what type of therapy they will need. "As you're dealing with a population, it's like dealing with a roulette wheel," he said.

Creating the Team Concept

Cox was in private practice for more than 25 years before joining UT Southwestern as medical director of oncology services at Parkland Health and Hospital System. He agreed with Page that the challenges of adjusting to the shift from FFS are very real. "The external forces in healthcare, they aren't going away, and they are only going to become more complex," he said.

A solution comes from learning to practice in teams and creating high expectations to go along with the use of data that drive APM insurance contracts. But things like risk stratification of the patient population start with a staff that embraces this process. "Beyond the mechanisms of doing this, of paying attention to the data, the change that is greatest in healthcare is managing people and expectations," Cox said.

"When you think about change management, this is often viewed as the soft stuff that gets put off at the end of the day," he said. But Cox said that is shortsighted. Putting the right people in the right roles is critical to a practice's success under an APM, which relies on nurses and nonclinical staff embracing their roles for everything from nutrition counseling to survivorship planning.

"To be successful in the world of APMs, we are going to have to pay a lot more attention to these leadership structures," Cox said. "That may require some hard decisions in your organization."

Metrics play a role in measuring who is thriving in their team function and who is not, and this can promote change. The key players are strong leaders who can cut through the silos that have traditionally defined cancer care and express a shared vision. "Culture eats strategy for lunch," he said.

A project by the American Society of Clinical Oncology (ASCO) and the National Cancer Institute brought together 21 teams that submitted vignettes on applying team principles to oncology practices. The need for teams to work interdependently came through, and the results were published.[4]

Teams are essential in today's environment, Cox said, given the "soul-sucking" challenges that confront physicians. Science and

therapeutic discussions are often limited by social determinants of health, "when patients don't have access to care," and clinicians lack the mechanisms to address these issues.

Getting Everyone on Board

In his South Carolina practice, Patel knew moving to the OCM would take every employee doing their part—no contribution could be wasted. Going in, he said, "the human potential was the least utilized aspect."

Making every employee a stakeholder in the shift was essential, and that occurred over a series of workshops that put every staff member on a level playing field to offer ideas. One person brought yoga into the practice. A receptionist took on additional duties, gained an additional certification, and got a significant raise.

Helping patients qualify for assistance through local agencies became a focus. The practice identified patients in need of dual eligibility status (Medicare and Medicaid) and helped them become qualified.

But the big target was keeping patients out of the emergency department (ED), and this required many steps: education, a rethinking of practice patterns, and a partnership.

"We started keeping 2 spots open every day at 2 locations, and we hired a [physician's assistant] to take care of that," Patel said. The practice also partnered with a local urgent care clinic and taught patients to go there first if they needed care after hours.

"Our physicians' quality of life has improved, because they didn't get as many after-hour calls," Patel said.

At all times, the practice paid attention to evidence blocks and even started an in-house clinical trial. Patel is a big believer in using biosimilars, and he educated patients about their use to achieve cost savings.

Patel presented data that show impressive results relative to other OCM practices: His practice's inpatient admissions are 31.9% lower, unplanned readmissions within 30 days of discharge are 37.8% lower, and ED visits not leading to admission or observation are 28.7% lower.

Doing the right thing turned out to be not only good for patients, but also good for the bottom line, he said. "We're focusing on true patient-centered care by living that dream every day—to reduce the overall cost of care, improve patient status, and get some savings back."

The Promise of Artificial Intelligence

If Page has been frustrated by the "roulette wheel" of the OCM, his CEO, Russo, was excited about a tool that may tell the clinical team where to place their bets.

Artificial intelligence (AI) is doing more than crunching reams of data, Russo said. It has the promise of using all that data to help oncology practices predict which patients are at risk of a 30-day readmission, who will need pain management, who are at risk of depression within the next 6 months—and even which ones face higher mortality risk.

CCBD is currently working with the healthcare startup Jvion on a risk-stratification pilot that Russo said could be transformative for clinicians who have been frustrated by the lack of utility in EHRs, which he said "are just a repository—you put a bunch of stuff in and nothing comes out."

AI can take all of those records and understand things like where adverse reactions could occur. In radiology, it can perform "second reads" of a scan. It can digest the data constantly emerging from scientific journals that no doctor has time to read and apply that information to a patient's case. He sees AI as having potential to speed up hospital consults or help payers examine similar patients who took a drug when someone receives a prescription for a new cancer therapy.

Russo said AI can even go through a patient's clinical record and find all applicable clinical trials and put those choices in front of the research team. "Do you know what a difference that could make in a patient's life? That's huge," he said.

The uselessness of the EHR in its current form, with data trapped in machines, has been a huge source of physician burnout. Russo sees AI as a tool that could turn this situation around, that could become an extension of what has been happening with clinical pathways. "The machine is not there to make your decision," he said to the clinicians. "The machine is there to put options in front of you."

To the point that Page made earlier about reconnecting doctors and patients, Russo sees AI as a huge time saver in the near future. Things like molecular testing results would eventually feed into the system. "It reduces some of the bumps along the way and reduces the chasm between the physician and the patient. All this stuff would eventually show up at the point of care."

> **"We started keeping 2 spots open every day at 2 locations, and we hired a [physician's assistant] to take care of that...Our physicians' quality of life has improved, because they didn't get as many after-hour calls."**
>
> —Kashyap Patel, MD, ABOIM, BCMAS

He sees potential to help get better analytics at the population level, to reduce the staff time it takes to understand the drivers of cost within each practice. If claims data could be fed into the system and AI could do the thinking, he said, "I can't even begin to tell you how much better the process would be for us to make changes to the organization."

Using Data to Achieve the Quadruple Aim

The rise of data in healthcare should be working for doctors and not against them. That's a principle of StratiFi Health, whose president of pharmacy solutions, Willoughby outlined the company's mission of doing the things that Page, Cox, Patel, and Russo talked about—restoring doctor–patient relationships, creating better solutions for population health management, improving team communication, and rebuilding physician morale. This last part has been added to the well-known triple aim of better health, better experience of care, and lower costs,[5] for a newer concept known as the quadruple aim.[6]

Fragmentation in healthcare frustrates everyone involved, Willoughby said. "We have so many disparate messages with no coordinated message that degrades the quality of care and raises the cost of care." ◆

RUSSO

Barry Russo is the chief executive officer of the Center for Cancer and Blood Disorders.

WILLOUGHBY

Tony Willoughby, PharmD, is the president of pharmacy solutions and co-founder of Thrive Pharmacy Solutions at StratiFi Health.

PATEL

Kashyap Patel, MD, ABOIM, BCMAS, is the president of Carolina Blood and Cancer Care Associates. He is also the associate editor of EBO™.

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#1 PRESCRIBED THERAPY IN FRONTLINE* AND PREVIOUSLY TREATED CLL[1†]

TAKE CONTROL OF CLL/SLL WITH YOUR FIRST STEP: IMBRUVICA® (ibrutinib)

Proven results across key efficacy endpoints: PFS and OS[2]

*Based on market share data from IMS from November 2016 to February 2018.
†Based on market share data from IMS from July 2014 to February 2018.

CLL
SLL

IMBRUVICA® (ibrutinib) is a kinase inhibitor indicated for the treatment of adult patients with:
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)[2]
- CLL/SLL with 17p deletion[2]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in 3% of patients, with fatalities occurring in 0.3% of 1,011 patients exposed to IMBRUVICA® in clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 44% of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood.

IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding.

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

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 24% of 1,011 patients exposed to IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA®.

Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA® therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,011 patients exposed to IMBRUVICA® in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension: Hypertension has occurred in 12% of 1,011 patients treated with IMBRUVICA® in clinical trials with a median time to onset of 5 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Second Primary Malignancies: Other malignancies (9%) including non-skin carcinomas (2%) have occurred in 1,011 patients treated with IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA® therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions.

Monitor patients closely and treat as appropriate.

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 10/18 PRC-04536

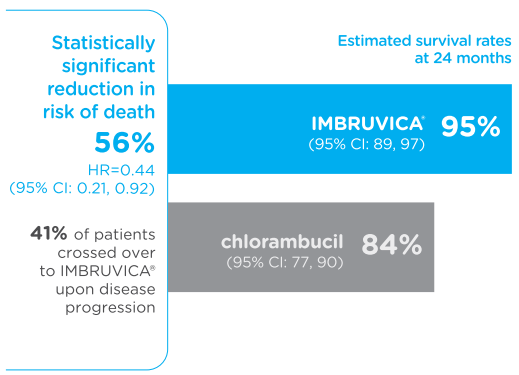
RESONATE™-2 FRONTLINE DATA

RESONATE™-2 was a multicenter, randomized 1:1, open-label, Phase 3 trial of IMBRUVICA® vs chlorambucil in frontline CLL/SLL patients ≥65 years (N=269)[2,3] Patients with 17p deletion were excluded[3]

EXTENDED OVERALL SURVIVAL[2]

SECONDARY ENDPOINT: OS
IMBRUVICA® vs CHLORAMBUCIL

Reduced risk of death by more than half

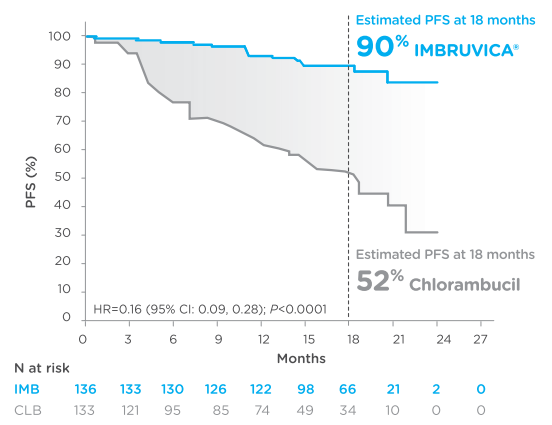


- Median follow-up was 28 months[2]
- Fewer deaths with IMBRUVICA® were observed; 11 (8.1%) in the IMBRUVICA® arm vs 21 (15.8%) in the chlorambucil arm[2]

PROLONGED PROGRESSION-FREE SURVIVAL[2,3]

PRIMARY ENDPOINT: PFS
IMBRUVICA® vs CHLORAMBUCIL

84% statistically significant reduction in risk of progression or death[2,3]



- Median follow-up was 18 months[3]
- With IMBRUVICA®, median PFS was not estimable vs 18.9 months (95% CI: 14.1, 22.0) with chlorambucil[2]
- PFS and ORR (CR and PR) were assessed by an IRC according to the revised 2008 iwCLL criteria[3]

RESONATE™-2 Adverse Reactions ≥15%

- Diarrhea (42%)
- Musculoskeletal pain (36%)
- Cough (22%)
- Rash (21%)
- Bruising (19%)
- Peripheral edema (19%)
- Pyrexia (17%)
- Dry eye (17%)
- Arthralgia (16%)
- Skin infection (15%)

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of therapy. 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. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (58%)*, neutropenia (58%)*, diarrhea (42%), anemia (39%)*, rash (31%), musculoskeletal pain (31%), bruising (31%), nausea (28%), fatigue (27%), hemorrhage (23%), and pyrexia (20%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (36%)*, thrombocytopenia (15%)*, and pneumonia (10%).

Approximately 7% of patients discontinued IMBRUVICA® due to adverse reactions. Adverse reactions leading to discontinuation included hemorrhage (1.2%), atrial fibrillation (1.0%), pneumonia (1.0%), rash (0.7%), diarrhea (0.6%), neutropenia (0.6%), sepsis (0.5%), interstitial lung disease (0.3%), bruising (0.2%), non-melanoma skin cancer (0.2%), and thrombocytopenia (0.2%). Eight percent of patients had a dose reduction due to adverse reactions.

*Treatment-emergent decreases (all grades) were based on laboratory measurements and adverse reactions.

DRUG INTERACTIONS

CYP3A Inhibitors: Dose adjustments may be recommended.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe baseline hepatic impairment. In patients with mild or moderate impairment, reduce IMBRUVICA® dose.

Please see the Brief Summary on the following pages.

CI=confidence interval, CLL=chronic lymphocytic leukemia, HR=hazard ratio, IRC=Independent Review Committee, iwCLL=International Workshop on CLL, OS=overall survival, PFS=progression-free survival, SLL=small lymphocytic lymphoma.

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To learn more, visit
IMBRUVICAHCP.com

imbruvica®
(ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use
IMBRUVICA® (ibrutinib) tablets, for oral use

INDICATIONS AND USAGE

Mantle Cell Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial *[see Clinical Studies (14.1) in Full Prescribing Information]*.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.

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

Marginal Zone Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.

Accelerated approval was granted for this indication based on overall response rate *[see Clinical Studies (14.4) in Full Prescribing Information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Chronic Graft versus Host Disease: IMBRUVICA is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 3% of patients, with fatalities occurring in 0.3% of 1,011 patients exposed to IMBRUVICA in clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 44% of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding *[see Clinical Studies (14) in Full Prescribing Information]*.

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 24% of 1,011 patients exposed to IMBRUVICA in clinical trials. *[see Adverse Reactions]*. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA.

Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,011 patients exposed to IMBRUVICA in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. See Additional Important Adverse Reactions.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

Hypertension: Hypertension has occurred in 12% of 1,011 patients treated with IMBRUVICA in clinical trials with a median time to onset of 5 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Second Primary Malignancies: Other malignancies (9%) including non-skin carcinomas (2%) have occurred in 1,011 patients treated with IMBRUVICA in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. 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 *[see Use in Specific Populations]*.

ADVERSE REACTIONS

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

- Hemorrhage *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Cytopenias *[see Warnings and Precautions]*
- Cardiac Arrhythmias *[see Warnings and Precautions]*
- Hypertension *[see Warnings and Precautions]*
- Second Primary Malignancies *[see Warnings and Precautions]*
- Tumor Lysis Syndrome *[see Warnings and Precautions]*

Clinical Trials Experience: Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Mantle Cell Lymphoma: The data described below reflect exposure to IMBRUVICA in a clinical trial (Study 1104) that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of ≥ 10% are presented in Table 1.

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with MCL (N=111)

	Percent of Patients (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9

* Based on laboratory measurements and adverse reactions

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure in one single-arm, open-label clinical trial (Study 1102) and three randomized controlled clinical trials (RESONATE, RESONATE-2, and HELIOS) in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1102 included 51 patients with previously treated CLL/SLL, RESONATE included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, RESONATE-2 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil, and HELIOS included 578 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab.

The most commonly occurring adverse reactions in Studies 1102, RESONATE, RESONATE-2, and HELIOS in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1102, RESONATE, RESONATE-2, and HELIOS discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1102: Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102 (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies*	12*	0
Vascular disorders	Hypertension	16	8

* One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

	Percent of Patients (N=51)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	69	12
Neutrophils Decreased	53	26
Hemoglobin Decreased	43	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

RESONATE: Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in RESONATE in patients with previously treated CLL/SLL.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and administration site conditions				
Pyrexia	24	2	15	1
Infections and infestations				
Upper respiratory tract infection	16	1	11	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

RESONATE-2: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in RESONATE-2.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0

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Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2 (continued)

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Eye disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular disorders				
Hypertension*	14	4	1	0
Nervous system disorders				
Headache	12	1	10	2

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

HELIOS: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in HELIOS in patients with previously treated CLL/SLL.

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	55
Thrombocytopenia*	34	16	26	16
Skin and subcutaneous tissue disorders				
Rash*	32	4	25	1
Bruising*	20	<1	8	<1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal pain	12	1	8	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular disorders				
Hemorrhage*	19	2	9	1
Hypertension*	11	5	5	2
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
Hyperuricemia	10	2	6	0

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
<1 used for frequency above 0 and below 0.5%

Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo +BR.

Waldenström's Macroglobulinemia and Marginal Zone Lymphoma: The data described below reflect exposure to IMBRUVICA in three single-arm open-label clinical trials (Study 1118, Study 1121, and INNOVATE monotherapy arm) and one randomized controlled trial (INNOVATE) in patients with WM or MZL, including a total n=307 patients overall and n=232 patients exposed to IMBRUVICA. Study 1118 included 63 patients with previously treated WM who received single agent IMBRUVICA. Study 1121 included 63 patients with previously treated MZL who received single agent IMBRUVICA. INNOVATE included 150 patients with treatment naïve or previously treated WM who received IMBRUVICA or placebo in combination with rituximab. The INNOVATE monotherapy arm included 31 patients with previously treated WM who failed prior rituximab-containing therapy and received IMBRUVICA.

The most commonly occurring adverse reactions in Studies 1118, 1121, and INNOVATE (≥ 20%) were thrombocytopenia, diarrhea, bruising, neutropenia, musculoskeletal pain, hemorrhage, anemia, rash, fatigue, and nausea.

Seven percent of patients receiving IMBRUVICA across Studies 1118, 1121, and INNOVATE discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were atrial fibrillation, interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 13% of patients.

Study 1118 and INNOVATE Monotherapy Arm: Adverse reactions and laboratory abnormalities described below in Tables 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in Study 1118 and 33 months in the INNOVATE Monotherapy Arm.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	38	2
	Nausea	21	0
	Stomatitis*	15	0
	Constipation	12	1
	Gastroesophageal reflux disease	12	0
Skin and subcutaneous tissue disorders	Bruising*	28	1
	Rash*	21	1
Vascular disorders	Hemorrhage*	28	0
	Hypertension*	14	4
General disorders and administrative site conditions	Fatigue	18	2
	Pyrexia	12	2
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	21	0
	Muscle spasms	19	0
Infections and infestations	Upper respiratory tract infection	19	0
	Skin infection*	18	3
	Sinusitis*	16	0
	Pneumonia*	13	5
Nervous system disorders	Headache	14	0
	Dizziness	13	0
Respiratory, thoracic and mediastinal disorders	Cough	13	0

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 10: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

	Percent of Patients (N=94)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	38	11
Neutrophils Decreased	43	16
Hemoglobin Decreased	21	6

INNOVATE: Adverse reactions described below in Table 11 reflect exposure to IMBRUVICA + R with a median duration of 25.8 months and exposure to placebo + R with a median duration of 15.5 months in patients with treatment naïve or previously treated WM in INNOVATE.

Table 11: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with WM in INNOVATE

Body System Adverse Reaction	IMBRUVICA + R (N=75)		Placebo + R (N=75)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Bruising*	37	1	5	0
Rash*	24	1	11	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	35	4	21	3
Arthralgia	24	3	11	1
Muscle spasms	17	0	12	1
Vascular disorders				
Hemorrhage*	32	3	17	3
Hypertension*	20	13	5	4
Gastrointestinal disorders				
Diarrhea	28	0	15	1
Nausea	21	0	12	0
Dyspepsia	16	0	1	0
Constipation	13	1	11	1
Infections and infestations				
Pneumonia*	19	13	5	3
Skin infection*	17	3	3	0
Urinary tract infection	13	0	0	0
Bronchitis	12	3	7	0
Influenza	12	0	7	1
Viral upper respiratory tract infection	11	0	7	0
General disorders and administration site conditions				
Peripheral edema	17	0	12	1
Respiratory, thoracic, and mediastinal disorders				
Cough	17	0	11	0
Blood and Lymphatic System Disorders				
Neutropenia*	16	12	11	4
Cardiac Disorders				
Atrial fibrillation	15	12	3	1
Nervous system disorders				
Dizziness	11	0	7	0
Psychiatric disorders				
Insomnia	11	0	4	0
Metabolism and nutrition disorders				
Hypokalemia	11	0	1	1

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Grade 3 or 4 infusion related reactions were observed in 1% of patients treated with IMBRUVICA + R.

Study 1121: Adverse reactions and laboratory abnormalities described below in Tables 12 and 13 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

Table 12: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 1121 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	43	5
	Nausea	25	0
	Dyspepsia	19	0
	Stomatitis*	17	2
	Abdominal pain	16	2
	Constipation	14	0
	Abdominal pain upper	13	0
	Vomiting	11	2
General disorders and administrative site conditions	Fatigue	44	6
	Peripheral edema	24	2
	Pyrexia	17	2
Skin and subcutaneous tissue disorders	Bruising*	41	0
	Rash*	29	5
	Pruritus	14	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	40	3
	Arthralgia	24	2
	Muscle spasms	19	3
Infections and infestations	Upper respiratory tract infection	21	0
	Sinusitis*	19	0
	Bronchitis	11	0
	Pneumonia*	11	10
Metabolism and nutrition disorders	Decreased appetite	16	2
	Hyperuricemia	16	0
	Hypoalbuminemia	14	0
	Hypokalemia	13	0
Vascular disorders	Hemorrhage*	30	0
	Hypertension*	14	5
Respiratory, thoracic and mediastinal disorders	Cough	22	2
	Dyspnea	21	2
Nervous system disorders	Dizziness	19	0
	Headache	13	0
Psychiatric disorders	Anxiety	16	2

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 13: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with MZL in Study 1121 (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	49	6
Hemoglobin Decreased	43	13
Neutrophils Decreased	22	13

Chronic Graft versus Host Disease: The data described below reflect exposure to IMBRUVICA in an open-label clinical trial (Study 1129) that included 42 patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy.

The most commonly occurring adverse reactions in the cGVHD trial (≥ 20%) were fatigue, bruising, diarrhea, thrombocytopenia, stomatitis, muscle spasms, nausea, hemorrhage, anemia, and pneumonia. Atrial fibrillation occurred in one patient (2%) which was Grade 3.

Twenty-four percent of patients receiving IMBRUVICA in the cGVHD trial discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were fatigue and pneumonia. Adverse reactions leading to dose reduction occurred in 26% of patients.

Adverse reactions and laboratory abnormalities described below in Tables 14 and 15 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 14: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions	Fatigue	57	12
	Pyrexia	17	5
	Edema peripheral	12	0
Skin and subcutaneous tissue disorders	Bruising*	40	0
	Rash*	12	0
Gastrointestinal disorders	Diarrhea	36	10
	Stomatitis*	29	2
	Nausea	26	0
	Constipation	12	0
Musculoskeletal and connective tissue disorders	Muscle spasms	29	2
	Musculoskeletal pain*	14	5
Vascular disorders	Hemorrhage*	26	0
Infections and infestations	Pneumonia*	21	10
	Upper respiratory tract infection	19	0
	Sepsis*	10	10
Nervous system disorders	Headache	17	5
Injury, poisoning and procedural complications	Fall	17	0
Respiratory, thoracic and mediastinal disorders	Cough	14	0
	Dyspnea	12	2
Metabolism and nutrition disorders	Hypokalemia	12	7

The system organ class and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 15: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

	Percent of Patients (N=42)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	33	0
Neutrophils Decreased	10	10
Hemoglobin Decreased	24	2

Additional Important Adverse Reactions: *Cardiac Arrhythmias:* In randomized controlled trials (n=1377; median treatment duration of 14.0 months for patients treated with IMBRUVICA and 7.5 months for patients in the control arm), the incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.4% and of Grade 3 or greater was 0.2% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of atrial fibrillation and atrial flutter of any grade was 8% versus 2% and for Grade 3 or greater was 4% versus 0.4% in patients treated with IMBRUVICA compared to patients in the control arm.

Diarrhea: Diarrhea of any grade occurred at a rate of 40% of patients treated with IMBRUVICA compared to 19% of patients in the control arm. Grade 3 diarrhea occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. The median time to first onset was 21 days (range: 0 to 475) versus 47 days (range: 0 to 492) for any grade diarrhea and 77 days (range: 3 to 310) versus 194 days (range: 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 84% versus 88% had complete resolution, and 16% versus 12% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 6 days (range: 1 to 655) versus 5 days (range: 1 to 367) for any grade diarrhea and 6 days (range: 1 to 78) versus 19 days (range: 1 to 56) for Grade 3 diarrhea in IMBRUVICA-treated subjects compared to the control arm, respectively. Less than 1% of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 12% of patients treated with IMBRUVICA (10% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 6% in the control arm (5% Grade 1 and <1% Grade 2 and 3). The median time to first onset was 96 days (range, 0 to 617) versus 109 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 61% versus 71% had complete resolution and 39% versus 29% had not reported resolution at the time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution was 31 days (range, 1 to 457) versus 29 days (range, 1 to 253) in IMBRUVICA-treated subjects compared to the control arm, respectively.

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

- Hepatobiliary disorders: hepatic failure including acute and/or fatal events, hepatic cirrhosis
- Respiratory disorders: interstitial lung disease
- Metabolic and nutrition disorders: tumor lysis syndrome *[see Warnings & Precautions]*
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), onychoclasis, panniculitis
- Infections: hepatitis B reactivation

DRUG INTERACTIONS

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

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

Effect of CYP3A Inducers on Ibrutinib: The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy: *Risk Summary:* IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities *(see Data)*. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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.

Data: Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or MZL and 20 times the exposure in patients with CLL/SLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

Lactation: *Risk Summary:* There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

Females and Males of Reproductive Potential: *Pregnancy Testing:* Verify the pregnancy status of females of reproductive potential prior to initiating IMBRUVICA therapy.

Contraception: Females: Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. 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 IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

Pediatric Use: The safety and effectiveness of IMBRUVICA in pediatric patients has not been established. Pediatric studies have not been completed.

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Geriatric Use: Of the 1011 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 22% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades) and Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA.

Hepatic Impairment: Avoid use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.

Dose modifications of IMBRUVICA are recommended in patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients for adverse reactions of IMBRUVICA closely *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

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

PATIENT COUNSELING INFORMATION

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

- *Hemorrhage:* Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions]*.
- *Infections:* Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Warnings and Precautions]*.
- *Cardiac Arrhythmias:* Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions]*.
- *Hypertension:* Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy *[see Warnings and Precautions]*.
- *Second primary malignancies:* Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions]*.
- *Tumor lysis syndrome:* Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions]*.
- *Embryo-fetal toxicity:* Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA *[see Warnings and Precautions]*.
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets approximately the same time each day *[see Dosage and Administration]*.
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose *[see Dosage and Administration]*.
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions]*. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions]*.
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration *[see Adverse Reactions]*.

Active ingredient made in China.

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Coverage by Mary Caffrey, Laura Joszt, and Jaime Rosenberg

NCCN Ovarian Cancer Guidelines Add Options for PARP Inhibitors, Bevacizumab

THE FIELD OF OVARIAN CANCER has come a long way over the past decade, David O'Malley, MD, of The James Cancer Hospital and Solove Research Institute at The Ohio State University Comprehensive Cancer Center, reminded attendees of the National Comprehensive Cancer Network (NCCN) 2019 Annual Conference.

He opened his talk with a slide of the first ovarian cancer guideline, issued in 2007. "It was all on 1 page," he said. "There wasn't much for us to do."

By contrast, the newest guidelines, updated in March, cover 126 pages. "In the last 10 years we've seen an unprecedented time of drug development. We've had more agents and more indications in 5 years than in the previous 50 years," O'Malley said.

The big news involves 2 areas: new uses for the antivascular therapy bevacizumab (Avastin) and approvals in ovarian cancer for poly (ADP-ribose) polymerase (PARP) inhibitors, targeted therapies that kill cancer cells by blocking enzymes that let the cells repair DNA. These therapies are effective in patients who have certain genetic mutations, including *BRCA1/2*. There are now 3 FDA-approved PARP inhibitors in ovarian cancer: olaparib (Lynparza), niraparib (Zejula), and rucaparib (Rubraca).

Findings that include GOG 218,[1] SOLO-1,[2] and ARIEL3[3] and subsequent FDA approvals have O'Malley questioning assumptions about the treatment of ovarian cancer, which the CDC still ranks as the fifth leading cause of cancer death for women. However, median survival has increased from less than 3 years to 5 years, he said.

"Is maintenance treatment curing people? I used to say no, but we may have to look at that," O'Malley said. "Can we cure people after recurrence? I used to tell people no, but I need to question my counseling."

Major updates in maintenance therapy

The guidelines make several updates in maintenance therapy in stage II, III, and IV disease.

Olaparib is recommended as first-line maintenance therapy for patients with *BRCA1/2* mutations in complete clinical remission or partial remission. The recommendation is category 1 for germline mutations and category 2B for somatic mutations; O'Malley said this occurred because there were so few patients with somatic mutations studied. The recommendation applies whether or not the patient was previously treated with bevacizumab.

The recommendation for olaparib is based on results from the SOLO-1 trial, which evaluated progression-free survival (PFS) based on RECIST criteria and found that median PFS was not reached in the olaparib arm compared with 13.8 months in the placebo arm (hazard ratio [HR] 0.30; 95% CI, 0.23-0.41; P <.0001).[2] Bevacizumab is also recommended for maintenance therapy postremission for patients with partial or complete responses who received it in primary treatment or for patients with stable disease.

Updates for bevacizumab were based on the GOG 218[1] and the ICON7[4] trials, which O'Malley reviewed. GOG 218 was cited in the June 13, 2018, FDA approval for bevacizumab in combination with paclitaxel or carboplatin, followed by bevacizumab as a single agent, for stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer after initial resection.[5]

The GOG 218 trial randomized 1873 women into 3 groups: The control group took chemotherapy and had a median PFS of 10.3 months; a second group started bevacizumab with chemotherapy but stopped, and PFS was 11.2 months; the third group continued with bevacizumab throughout treatment. The HR for progression to death relative to the control group was 0.717 for those treated with bevacizumab throughout (95% CI, 0.625-0.824; P <0.001).[1]

In reviewing the ICON7 results, O'Malley noted that although the overall results for did not reach statistical significance, bevacizumab was very effective for the highest-risk patients; published results show that the estimated median PFS was 10.5 months with standard therapy versus 15.9 months with bevacizumab (HR, 0.68; 95% CI, 0.55-0.85; P <.001).[4]

Persistent and resistant disease and recurrence

If patients have platinum-sensitive disease and relapse more than 6 months after completing chemotherapy, a new algorithm in the guidelines calls for 2 platinum therapies (a platinum doublet), possibly alongside bevacizumab or a PARP inhibitor. The algorithm allows these options if patients with advanced cancer are in complete or partial response to platinum-based chemotherapy. All 3 PARP inhibitors—olaparib, rucaparib, and niraparib—are listed. In support of these updates, O'Malley presented findings from the OCEANS trial[6] involving bevacizumab with carboplatin and gemcitabine, the GOG 213 trial,[7] and separate trials involving each PARP inhibitor.

Rucaparib received FDA approval for this indication in April 2018 based on results of the ARIEL3 trial, which found that median PFS for the overall study population was 10.8 months versus 5.4 months for placebo.[8] For patients in *BRCA*-mutated subgroups, the risk of progression to death fell 77%; median PFS was 16.6 versus 5.4 months (HR 0.23; 95% CI, 0.16-0.34; P <.0001). Niraparib received approval in this setting in 2017 based on the NOVA trial.[9]

Bevacizumab is also the centerpiece of regimens with nonplatinum combinations, O'Malley said, based on results from the 2014 AURELIA trial.[10]

Testing recommendations upgraded

As seen across the updated NCCN guidelines during the conference, the updated recommendations in ovarian cancer call for tumor molecular testing if not previously done. Validated molecular testing should include *BRCA1/2* and microsatellite instability or DNA mismatch repair, if not previously done. Homologous recombination deficiency testing can be considered.

Because a PARP inhibitor may be used, "all patients should have germline testing," O'Malley said. "But we should not delay therapy for testing." ◆

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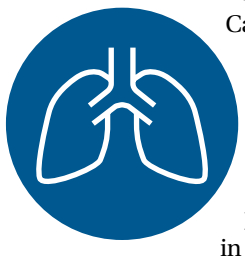
PD-L1 Testing "Name of the Game" in First-Line Treatment of NSCLC

THE WORD "GIDDY" WAS circled in a 2014 *New York Times* article that Matthew A. Gubens, MD, MS, referenced to start his update on the use of checkpoint inhibitors in non–small cell lung cancer (NSCLC). The thoracic oncologist reminded attendees of the National Comprehensive Cancer Network (NCCN) 2019 Annual Conference that less than 5 years have passed since the approval of pembrolizumab (Keytruda), the first cancer drug based on a tumor's characteristics rather than its location.



The giddy phase may be over. But Gubens, of the University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, said the excitement has given way to an immuno-oncology tsunami: 940 agents in clinical testing, 303 targets, 864 companies, and 3042 trials with enrollment of 577,076 patients.

Much of that progress has come in NSCLC, and Gubens presented new guidelines for first-line recommendations in immunotherapy and biomarker testing. Following Gubens, Marianne Davies, DNP, MSN, RN, CNS, ACNP-BC, AOCNP, of Yale Cancer Center, presented updates on strategies for managing adverse events.

"PD-L1 testing is really the name of the game," Gubens said, referring to assays that measure the level to which tumors overexpress the programmed death ligand 1 (PD-L1) protein. As Gubens explained, the KEYNOTE-024 trial showed that pembrolizumab in patients with NSCLC more than doubled median overall survival compared with chemotherapy if PD-L1 expression, making that level an important cut point in deciding on treatment. If PD-L1 expression is below 50%, decisions turn on whether the cancer is squamous or nonsquamous.

Several guidelines that took effect in January 2019[1] combine pembrolizumab with chemotherapy. Although this brings greater toxicity, Gubens said, clinicians and patients alike "will consider the higher disease burden with the idea that 'I want a response now; I may not get to second line.'"

With greater shared decision making, he said, savvier patients understand that choosing more aggressive therapies brings the higher response.

New guideline based on KEYNOTE-024. Pembrolizumab is preferred as first-line therapy for NSCLC when PD-L1 expression is 50% or greater. This is a category 1 guideline, which means there is uniform consensus that the intervention is appropriate. This guideline applies to both adenocarcinoma and squamous cell carcinoma.

New guideline based on KEYNOTE-189. What about PD-L1 expression of less than 50%? Gubens reviewed the KEYNOTE-189 results, a phase 3 trial that involved patients with metastatic nonsquamous NSCLC who had no prior treatment. Patients were randomized 2:1 to receive pemetrexed and a platinum-based chemotherapy plus either pembrolizumab or placebo. Patients could cross over if they progressed on the control arm. Although survival was more pronounced on those with 50% or greater PD-L1 expression, improved survival was seen across the board. Based on these results, the new guideline update adds the following as preferred category 1 initial systemic therapy options (ECOG performance status of 0-1) for advanced or metastatic adenocarcinoma in NSCLC (if no contraindications to adding pembrolizumab): pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed.

What if patients cannot take pemetrexed? Based on the guideline, Gubens said the best option for patients with adenocarcinoma in NSCLC is the next recommended category 1 combination, atezolizumab/carboplatin/paclitaxel/bevacizumab.

New guideline based on KEYNOTE-407. A study published in November 2018 in the *New England Journal of Medicine*, KEYNOTE-407, is reflected in the guideline update for combination therapies in squamous NSCLC. The preferred category 1 recommendations are pembrolizumab/carboplatin/paclitaxel or pembrolizumab/carboplatin/albumin-bound paclitaxel.

"Clinicians and patients alike will consider the higher disease burden with the idea that 'I want a response now; I may not get to the second line."

— Matthew A. Gubens, MD, MS

Biomarker testing. As important as PD-L1 testing is now, Gubens said, this is the just the beginning. He discussed the growing importance of understanding patients with high tumor mutation burden as a distinct population from those with high PD-L1 expression and said that forthcoming blood assays could be promising in predicting which immunotherapies will work. "In 5 years, PD-L1 might be archaic. Stay tuned for multidimensional and serial testing," he said, referring to tests that occur throughout cancer treatment, not just at the start.

Guidelines for Immune-Related Adverse Events

The overall NCCN guideline[2], Management of Immunotherapy-Related Toxicities, received a substantial update in January 2019 from its February 2018 version, notably adding a section on managing the effects of chimeric antigen receptor T-cell therapy. Davies focused on updates relating to adverse events (AEs) from checkpoint inhibitors in lung cancer, noting that onset can occur between 5 and 12 weeks and may take place concurrently or sequentially. "Every organ system in the body can be involved, and we need to be cognizant of that," she said.

Davies reviewed AEs from 8 recent trials (4413 patients with NSCLC) that contributed to the updates. She then discussed a meta-analysis that showed that 46.53% of patients had high-grade AEs from chemotherapy, including 13.92% who subsequently discontinued therapy; 14.26% of patients had high-grade AEs from PD-1/PD-L1 treatments, including 5.94% who stopped therapy because of AEs. Patient deaths attributable to AEs were seen in 1.12% of chemotherapy and 0.48% of PD-1/PD-L1 patients. By far, the most common AE was fatigue.

The guideline contains specific algorithms for dermatological, gastrointestinal, endocrine, pulmonary, renal, ocular, cardiovascular, and hepatic AEs, including when to temporarily or permanently discontinue immunotherapy or switch therapies. Steroids, both topical and prednisone, are frequently indicated; with long-term use, vitamin D and calcium are indicated. ◆

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NCCN Prostate Cancer Update Emphasizes Germline Testing

A MARCH 6, 2019, update[1] of the National Comprehensive Cancer Center (NCCN) guidelines for the treatment of prostate cancer included an emphasis on gathering family history and "more careful interrogation of germline mutations," according to James D. Mohler, MD, associate director and senior vice president of translational research at Roswell Park Comprehensive Cancer Center.

Mohler gave an overview of the guideline updates at the National Comprehensive Cancer Network (NCCN) 2019 Annual Conference in Orlando, Florida. He was joined by Emmanuel S. Antonarakis, MBBCh, an associate professor of oncology and urology at the Sidney Kimmel Comprehensive Cancer Center at John Hopkins Medicine, who discussed ways to integrate genetic testing into clinical practice.

As Mohler discussed, knowledge of the importance of family history in prostate cancer has increased since the 1990s; recent research findings show the importance of germline DNA repair abnormalities, notably *BRCA* mutations and Lynch syndrome. The mutations can manifest in a host of cancers, including breast, ovarian, and pancreatic (NCCN guideline updates in this disease also reflect knowledge gained about germline testing).

More testing recommended. The guidelines update calls for taking a family history immediately at diagnosis; along with prior recommendations to explore *BRCA* mutations and Lynch syndrome, a new one advises testing for the presence of intraductal carcinoma (IDC). Mohler cited work by Antonarakis that shows this is associated with aggressive disease. If a patient has a family history of mutations or IDC, germline testing is recommended, preferably with genetic counseling. If family history is unknown, testing may still be considered, based on clinical features.

The guidelines contain a risk stratification and staging workup for germline testing of clinically localized disease. Mohler said that clinicians can weigh next-generation sequencing (NGS) or targeted testing; if NGS is used, the panel must include *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, *PALB2*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*. NGS costs about $3500, and targeted testing is cheaper, he said.

"By using targeted testing, you could miss mutations that could affect the course of treatment later," he said. Mohler addressed the controversy over more widespread testing, noting that earlier this year,[2] the American Society of Breast Surgeons called for testing every diagnosed breast cancer patient with a multigene panel. "This is an area where we will have to pay close attention," he said.

Tumor testing. Antonarakis discussed updates that related to testing of the tumor itself; testing for microsatellite instability or deficient mismatch repair (MMR) could inform clinicians whether pembrolizumab is indicated as a second- or third-line therapy for adenocarcinoma in castration-resistant prostate cancer (CRPC), with or without visceral metastases. "The evidence is level 2B because there [are] no prospective data, yet we have an FDA approval," Antonarakis said, referring pembrolizumab's historic "site agnostic" approval. MMR mutations occur in 3% to 5% of metastatic CRPC (mCRPC) patients, he said. The guidelines also call for genetic counseling and germline testing for homologous recombination deficiency (HRD), which Antonarakis said occurs in 15% to 25% of mCRPC cases. Where HRD is found, investigational poly (ADP ribose) polymerase inhibitors can be considered, he said.

Patients with intermediate risk. The large, diverse group of patients classified as intermediate risk presents a challenge for clinicians developing treatment approaches. These patients are divided into "favorable" and "unfavorable" groups. The new guidelines say that for the favorable group, after initial therapy, observation is now preferred; for the unfavorable group, the following apply: Initial therapy changes from external beam radiation therapy (EBRT) + androgen deprivation therapy (ADT) for 4 to 6 months to EBRT ± ADT for 4 to 6 months, or initial therapy changes to EBRT + brachytherapy ± ADT for 4 to 6 months.

Mohler drilled down data comparing intermittent and continuous use of ADT intermittently and continuously; new language calls for considering intermittent ADT in M0 prostate-specific antigen cancer. He noted language now appearing in the guidelines: "Whether treatment of regional nodes in addition to the primary improves outcomes remains uncertain; nodal treatment should be performed in the context of a clinical trial."

> **"We need to start thinking about the cost of treatment or [financial] toxicity. We need good data in this field, and there [are] not a whole lot."**
>
> — James D. Mohler, MD

For metastatic castration-naïve disease, "ADT is the gold standard," the guideline reads, but a phase 3 trial comparing continuous with intermittent could not show noninferiority for survival. Quality of life was better in the intermittent arm.

Castration-Resistant Prostate Cancer. Updates also addressed secondary hormone therapy in nonmetastatic CRPC, or M0 CRPC. Mohler reviewed clinical trials that led to recommendations for apalutamide and enzalutamide, which appear in the guidelines, as well as a trial for darolutamide, which is not included because it is not yet approved.

A "rousing debate" centered on whether these therapies should become the new standard of care, said Mohler, who addressed the cost of the therapies. If a man is diagnosed with CRPC that becomes metastatic, the cost can easily run from $500,000 to $1 million.

"We need to start thinking about the cost of treatment or [financial] toxicity," Mohler said, noting that this is becoming an especially big problem for families of patients with prostate cancer. "We need good data in this field, and there [are] not a whole lot," he said. ◆

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Future of Biosimilars in Cancer Care Will Require a Balancing Act, Lyman Says

ACCEPTANCE OF BIOSIMILARS IN cancer care will require oncologists to demand just the right amount of data on these products, according to Gary Lyman, MD, MPH, of the Fred Hutchinson Cancer Research Center and the Seattle Cancer Care Alliance.

In a presentation during the 2019 National Comprehensive Care Network (NCCN) Annual Conference, Lyman said oncologists need enough data to feel comfortable that biosimilars work as well as their reference products, but they cannot expect so much that the cost savings will be wiped out.

"This would defeat one of the primary purposes of their development," Lyman explained. "But if we don't require enough [data] while making the approval process easier—prices will come down—it will lower our confidence that adequate due diligence has been done."

LYMAN

Finding that sweet spot remains a work in progress in the United States, where biosimilars have struggled, Lyman said. He encouraged the oncologists at the NCCN conference to look to the European experience as a guide. He noted that more than 25 biosimilars have been approved in the European Union since 2006, but the monitoring system had not identified "any relevant difference in the nature, severity, or frequency of adverse effects between biosimilar medicines and their reference medicines" in 10 years.

Both the FDA and the European Medicines Agency require ongoing monitoring of the manufacturing processes for all biologics, which Lyman said is essential to ensure quality and safety.

Biosimilars Are a Means to Improve Access

Much of Lyman's presentation was aimed at giving those unfamiliar with biosimilars an overview of why these biologics can offer patients access to innovative biologics, including those developed for cancer treatment. He presented data from IMS Health that show global spending on biologics continues to outpace that of spending on pharmaceuticals overall, reaching $221 billion in 2017.

He reviewed FDA evidence requirements for biosimilars as well as the March 2015 approval of the first US biosimilar, filgrastim, sold as Zarxio, a granulocyte colony-colony stimulating factor (G-CSF). Filgrastim biosimilars that reference the originator product, Neupogen, remain among the most common worldwide, although Lyman noted that there are other FDA-approved biosimilars of interest to the oncologist: 1 each for rituximab and bevacizumab and 4 different ones that reference trastuzumab.

He pointed to updated areas of the 2019 NCCN guidelines, using prostate cancer as an example, and showed where different G-CSF products are listed for treatment of neutropenia. The prostate cancer guideline included 2 biosimilar versions of a G-CSF, Zarxio and Nivestym, as well as tbo-filgrastim (Granix), which was approved before the biosimilar pathway existed. It also included 2 products that reference pegfilgrastim, Fulphila and Udenyca.

Lyman also took note of the 2018 FDA approval for Retacrit, which references epoetin alfa, a medication that stimulates erythropoiesis and is used to treat anemia that occurs in chronic kidney disease associated with chemotherapy. The NCCN update in prostate cancer states, "The panel extrapolates that there would be no clinically meaningful difference for treatment of [chemotherapy-induced anemia]."

Transparency Is Key

Lyman explained that physicians remain skeptical about biosimilars and fear that payers or health systems will force their use for cost reasons. The availability of strong clinical data will be essential to ensure that clinicians accept biosimilars, he said.

"NCCN is very concerned that we have access to the data that the FDA have," he said. Whether the guidelines committees get the data from the FDA or directly from the manufactures, Lyman said, it is essential to have this information so that biosimilars can be integrated into the guidelines going forward.

The naming convention is extremely important because if there are adverse effects, providers will know which biosimilar was used. "If we don't know or if our patients don't know what form of trastuzumab was used, that's an injustice to our patients," Lyman said.

He pointed to a May 2018 policy statement from the American Society of Clinical Oncology, for which he served as lead author, which discussed naming and regulatory considerations, safety and efficacy, interchangeability, switching, and substitution; the value of biosimilars; and provider and patient education.[1]

There's no question, Lyman said, that "biosimilars will be playing an important role." ◆

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The Art and Science of Talking About End-of-Life Care

TOBY G. CAMPBELL, MD, MSCI, is a thoracic oncologist and a palliative care physician from the University of Wisconsin Carbone Cancer Center. He began his talk during the final session of the 2019 National Comprehensive Cancer Network (NCCN) Annual Conference with a confession:

"I cannot practice palliative [care] and oncology very effectively at the same time."

There are moments, Campbell said, when "there is some blend and some blur" between his specialties, but the skill sets are distinctly different. Palliative care takes a different path from oncology and defines success differently.

CAMPBELL

The goal of his talk, "Navigating the Transition to End of Life Care in Patients With Cancer," was to help physicians take the dry language of the NCCN palliative care recommendation[1] to help patients "develop prognostic awareness" and turn that into what Campbell called "tools in the tool kit."

Ultimately, Campbell said, some patients will need a recommendation for hospice, and physicians need to know how to have that conversation. Historically, health systems in the United States have fared poorly at this; the 2015 Institute of Medicine report *Dying in America*[2] painted a bleak picture of fragmented care, overburdened families, and care that was often not what the patient wanted. CMS' Oncology Care Model seeks to address this by requiring every patient with cancer to have a survivorship care plan. But the challenge of the doctor–patient interaction remains because so many physicians were trained in an era when medical schools did not address end-of-life issues.

If the goal is "prognostic awareness," Campbell said, the conversation must start early. "If we're going to be talking about dying," he said, "it really is a conversation that's best done in bits and pieces."

Work at the University of Wisconsin is developing phrases to open the door. Phrases are tested—doctors even practice with actors—and once they are fine-tuned, the best methods are studied to measure their effectiveness. Campbell and his colleagues have learned that success

starts by laying the groundwork early because success can have a variety of outcomes.

He showed the audience a slide that plotted out a schedule of 8 appointments, which he said would give a physician a total of 4 hours to discuss palliative care. But more critically, each appointment affords an opportunity to start the conversation at home, during the "spaces in between," when the real thinking about goals and values takes place. "This will assist in the eventual conversation," he said.

Add the Question to Appointments

Campbell said the pattern of the typical oncology appointment is divided into 3 parts: discussions of symptoms, scans, and treatment. Analyses of conversations in the middle portion of the appointment, when physicians deliver news that the scans are "good," "stable," or "bad," show that this is the shortest part of the conversation; when news is bad, the treatment segment expands significantly.

Here, Campbell said, is where clinicians must use what he called the blend and "create the space to talk about dying." The method developed at the University of Wisconsin adds a step between the scan and treatment portions of the appointment to ask, "Would you like to talk about what that means?"

The question should be asked even if the news is good, because if treatment is working, it can extend life, but there could be adverse effects. The idea of shared decision making is critical so that patients and families will always understand available options.

Use Paper-and-Pencil Homework

The development of an "oncology talk tool" is a simple paper-and-pencil chart that shows options for patients and families to consider when one option is to stop treatment. Campbell showed samples of charts that clinicians created that included estimated odds, "0/10" for stopping treatment, followed by "1/10" for a chemotherapy option and "????" for entering a clinical trial. This "best case, worst case" scenario gives patients the critical information to take home and discuss with their families, Campbell said. "This is entirely about the spaces in between," he said.

In a study that included follow-up at patients' homes, even after some had died, many families still had the charts. "No one said, 'I hated that piece of paper they gave me,'" Campbell said.

With Hospice, the Order Matters

Campbell presented a framework for presenting hospice that begins with telling the patient, "I don't have any more good treatment options left." Instead of saying the word *hospice*, describe the nursing and social work services it offers. He suggested that physicians recommend the services first, as a way to give patients care to relieve pain and keep them out of the emergency department, and then say, "It's called hospice."

Through testing, Campbell said, "it appears the second strategy is more effective."

Campbell encouraged physicians to get the patient's buy-in, reminding them of statements made in previous conversations of their desire to manage pain at home and gaining their agreement to not pursue more treatment. The phrase "How does that sound to you?" is important.

Avoid euphemisms, he said. "The gold standard is to use the word *dying*."

The goal is to present hospice as a service available only to people in their circumstances, who want to "focus on living with the time remaining." Time spent at home with family, in as much comfort as possible as a conscious choice, helps patients realize they have what they need, Campbell said. ◆

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Aging Population, Rising Morbidity Add to Challenge of Survivorship

AMERICANS ARE LIVING LONGER after a cancer diagnosis. Survivorship guidelines are now a well-recognized part of the cancer care landscape; CMS' Oncology Care Model even requires that each Medicare beneficiary have a survivorship care plan.

That's the good news.

But there's bad news, too, according to a nurse and a primary care physician from the University of Colorado Cancer Center, who spoke at the 2019 National Comprehensive Cancer Network (NCCN) Annual Conference.

CALLAWAY

According to Carlin Callaway, DNP, RN, and Linda Overholser, MD, MPH, cancer survivors don't always do what they're told. About 50% don't wear sunscreen as advised, and 27% do not see a primary care provider (PCP) regularly. An increasing number of survivors have obesity, metabolic syndrome, and other health issues. They don't always eat healthy or exercise, even though this would increase their chances of survival.

In other words, cancer survivors are aging and come to the cancer journey with more and more comorbidities, just like the rest of the population. But this adds to the challenges of care coordination, what Callaway called "the invisible work" that happens when the care team—PCPs, oncologists, and specialists—works together to keep the patient's needs from falling through the cracks.

"People are living years with lung cancers, which is wonderful," said Callaway. "But how do they live with the hypothyroidism and the blood sugar challenges?"

A March 14, 2019, update of NCCN Guidelines for Survivorship includes a revised definition[1] that reflects the fact that guidelines apply throughout the continuum of care and to long-term survivors. Callaway said the University of Colorado advises patients to tell healthcare providers what cancer agents they were given; "for the duration of their life…adverse events may be delayed."

Immunotherapy has been a game changer for many patients, but it's not without costs—physical, emotional, and financial, Callaway noted. Intimacy and sexual health may be interrupted. "Our patients have many unmet needs when they finish treatment. Relationships may have changed, for better or for worse. Many people are able to return to work, but many are not."

The handoff back to the PCP can be emotional; some patients are ready for it, and some don't want to leave the oncologist. Then there's the matter of conflict among professional societies over follow-up care. For example, the NCCN recommends that women on tamoxifen have an annual gynecological assessment every 12 months if a uterus is present, but the American College of Obstetricians and Gynecologists (ACOG) says these women are at no increased risk of uterine cancer and require no additional monitoring beyond routine care, according to an ACOG guideline reaffirmed in 2019.

Survivorship care plans. Callaway said a good plan is simple and easy for the patient to use and the PCP and specialists to find within the electronic health record (EHR). The patient must have control over who sees the plan. Although evidence that survivorship plans improve quality of life is limited, Callaway cited a 2017 study by Spears et al that found when an advanced practice nurse administered the plan, there was an improvement in quality of life and cost-effectiveness. A study from Majhail et al found that plans can reduce stress. A significant review article[2] highlighting the benefits of cancer survivorship care, including care plans, appeared in the *New England Journal of Medicine* in December 2018.

The most basic truth about a care plan? "If patients understand their survivorship plans, they are more likely to use them," Callaway said.

Challenges ahead. As more patients live with cancer, Overholser said, more PCPs are getting questions about life after treatment. And they don't always feel equipped to answer them, she said, especially questions about the cancer treatment. More and more, PCPs are asked about the psychosocial decisions, and increasingly they deal with the cardiovascular and metabolic aftermath of some therapies.

The healthcare infrastructure must do more to facilitate the movement of patients and information back and forth between oncologists and primary care, Overholser said. There's not much formal training among PCPs in survivorship care, she said, and a 2017 study by Rubenstein et al found that in 12 advanced primary care practices, cancer survivors were not recognized as a unique subgroup and physicians could not easily identify survivors based on the EHR.

But the biggest challenge ahead is the rising rate of comorbidities. Overholser cited data from *BMJ Open* that show multimorbidity affects 23% of the general population, including 65% of those who are Medicare eligible. Among those with cancer, the most common conditions were cardiovascular and metabolic: diabetes, congestive heart failure, and cerebrovascular. Overholser said these conditions may be a bigger threat than cancer to long-term survival.

Again, there's good news and bad news. "Primary care only sees a handful of cancer survivors," Overholser said. But when it comes to obesity, metabolic syndrome, and high blood pressure, "these are the issues we see every day."

The most powerful tool that the entire care team has, Callaway said, is patient engagement. If providers can figure out how to harness the desired behaviors of patients, she said, it would be, as neuroscientist Leonard Kish[3] called it, "the blockbuster drug of the century." ◆

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Survey Reveals Different Vantage Points but Similar Goals of High-Value Care, Patient Satisfaction

A DIVERSE PANEL OF representatives from several practice models provided insights into what has and has not worked for them in their attempts to improve cancer care. The discussion took place at the Association of Community Cancer Centers' 45th Annual Meeting & Cancer Center Business Summit, held March 20 to 22 in Washington, DC.

The session kicked off with highlights from the recent Trending Now in Cancer Care survey. Deirdre Saulet, PhD, practice manager at The Advisory Board Company, noted that survey respondents—which included people at nonteaching community hospitals, academic medical centers, and freestanding cancer clinics—identified symptom management, including reduction of emergency department visits, and clinical standardization as 2 of the biggest opportunities for cost savings. Identifying these areas is critical, as healthcare may follow a fee-for-service model, but it is increasingly moving toward value-based or outcomes-based payments.

On the flip side, respondents said the biggest return on investment for cancer programs was care coordination, such as navigation.

"It's not…enough to attract patients to your program anymore. You really need to…shepherd them throughout the process [and] keep them loyal to your system," Saulet said.

Engaging and Empowering Providers

Each of the panelists described what their practice, program, or company does well. Linda Bosserman, MD, medical oncologist at City of Hope, highlighted the center's diversity. She noted City of Hope has community centers that are not under 340B, as well as a center that is under 340B; the ability to bring together community oncologists and oncologists in the academic center to compare outcomes; and the push to bring surgeries, research, and treatment closer to the patient at home through telemedicine.

OptumCare Cancer Care, a division of OptumCare, which is a subsidiary of UnitedHealthcare, is developing a multispecialty entity with surgery, radiation oncology, and medical oncology that practices quality care, follows guidelines from the National Comprehensive Cancer Network, and focuses on patient satisfaction, according to Russell Goddard, MD, director of medical oncology. The center is instituting a collaborative approach among nutritionists, psychologists, and palliative care doctors early in a patient's cancer journey.

"I think we're nimble enough that we can react fast, we can see what some of the issues are, we get a lot of really direct feedback from patients because of the nature of our relationship … and I think that generates, ultimately, for us, a better product."

— Barry Russo, chief executive officer, The Center for Cancer and Blood Disorders

As a community practice, The Center for Cancer and Blood Disorders really knows its patients and their experience and what the center can implement to improve that experience, explained Barry Russo, chief executive officer. When the practice noticed it had an issue with palliative care, it pulled in a palliative care expert; when it realized socioeconomic issues were significant for patients, it engaged social workers, dieticians, and others.

"I think we're nimble enough that we can react fast, we can see what some of the issues are, we get a lot of really direct feedback from patients because of the nature of our relationship…and I think that generates, ultimately, for us, a better product," Russo said.

Meanwhile, OneOncology, a new organization comprising 3 leading oncology practices—Tennessee Oncology, New York Cancer & Blood Specialists, and West Cancer Center—is empowering physicians in the community and physician-led community oncology practices to succeed. Erich A. Mounce, MSHA, chief operating officer at OneOncology, explained that the organization helps community oncologists gain access to capital, technology, and expertise so they can compete with other entities, including academic institutions and giant not-for-profit hospitals.

"For us, the best care is delivered in the community setting, no matter what, and that's what we aim to continue," Mounce said.

Inova Schar Cancer Institute recognized in 2014 that it had few closely associated practices and made a commitment to change based on the realization that the future of cancer care was ambulatory, said Donald L. "Skip" Trump, MD, FACP, chief executive officer and executive director at Inova. Since then, the institute has made progress, developing a model that attempts to be patient centric by listening to patients and putting into place modern technology.

The goal, said Roger Brito, DO, national director of oncology at Aetna, is to be able to use all these different network and practice models to focus on improving patient care overall. No one model is necessarily better than the other—they should be used together, according to Brito.

Saulet added that communication and coordination among each of the groups are crucial and that, as a patient, she wants to know that her providers

are all talking and delivering cost-effective, patient-centered care in the appropriate setting.

Room for Change: Care Coordination, Cost Control, Technology

However, no company, practice, or organization is perfect, and moderator Michael Kolodziej, MD, FACP, vice president and chief innovation officer at ADVI, challenged the panelists to acknowledge what they do poorly and need to improve upon.

Trump highlighted the difficulty Inova faced in getting everyone on the same page; Mounce discussed the need for better investment in the workforce; Russo explained that coordination across specialties was difficult, especially with everyone under different reimbursement structures; Goddard pointed to the jigsaw puzzle of providing quality and cost control in a population health model and getting true provider engagement; Russo identified the need for technology support that notifies the practice when a patient enters the emergency department or the outpatient setting; and Bosserman described the challenge of getting molecular data to the bedside and into the fingers of experts in real time.

The panelists finished with a discussion of the Oncology Care Model (OCM). With the exception of Brito, they all believed OCM would continue, perhaps with some evolutionary changes.

Although OCM is not perfect, it has pushed oncologists to examine several aspects of the care process that they were not previously addressing, Russo said. However, his practice has struggled with the model. Despite having a cost of care per case that is on a downward trajectory, The Center for Cancer and Blood Disorders has not been financially successful under the model.

Mounce agreed, saying that OCM has allowed oncology to focus on things they needed to focus on, such as coordinating care, investing in the care of patients throughout their entire journey, and understanding how to incorporate palliative care earlier.

Although Brito thinks OCM makes sense conceptually, he said he does not like the data dumps that go to providers, because they struggle to make sense of the information they receive. In addition, the current model does not do a good job of accounting for novel therapies, said Brito.

"As we look at the data, as [they start] to mature, what we're seeing is we need to come up with a 2.0, 3.0 strategy because the immunotherapy agents changed the game," Brito said. ◆

Envisioning the Future of Cancer Care

"WE DON'T NEED NEW sights; we need new eyes," said healthcare futurist Joe Flower as he opened up the Association of Community Cancer Centers' 45th Annual Meeting & Cancer Center Business Summit, with a vision of a healthcare system that provides better quality care at a lower cost and is more easily accessible to all stakeholders.

Healthcare is complex, so simple solutions will not work, Flower said. And over the next 10 years, the healthcare industry will experience a turbulent time as a result of multiple factors, ranging from new technologies to economic pressures.

The goal is to remove the current fee-for-service, opaque system and replace it with one that is more efficient and transparent. Those who lead the charge on this will be more attuned to the needs of the market and will excel at building and reshaping the business of care seriously and deeply around the needs of patients and their families, as well as the emerging big buyers of healthcare, Flower said.

Before painting a picture of how the healthcare system could—and should—look in the future, Flower homed in on why these changes are being sought after. The central factor driving all the change the community is seeing, and will continue to see, in healthcare is that it costs too much, he said. This year alone, the United States will spend an estimated $3.9 trillion on healthcare, approximately one-third of which will be waste. And cancer care is the poster child for the extraordinarily shocking cost of healthcare in the country, he said.

Looking at trends over time, Flower pointed out that US healthcare spending started to increase faster than that of other countries in 1983-1984, when diagnosis-related group codes were implemented. Although they were meant as a cost-cutting measure, these codes in effect gave "the industry a manual for how they can make more money" by upcoding and using newer technology with a better *International Classification of Diseases, Ninth Revision*, code even if the technology was not more expensive, he said.

Flower then presented the audience with a table of elements, including all the facets he said are needed to facilitate this care delivery transformation the industry so often hears about.

"Community cancer centers are generally ahead of the rest of healthcare in these areas because of the nature of cancer care," said Flower. "In the changed environment, you can look to community cancer centers' relative skill in these areas as a competitive advantage."

This new care delivery system begins with behaviors driving such an environment, notably trust, which includes trust between patient and provider as well as among different members of the care team. He also mentioned the phrase commonly cited when envisioning the future of cancer care: *patient-centered care*, in which the system is built around the patient's needs. Other drivers include moving from acute treatment to chronic, longitudinal treatment, as well as population heath and community health strategies.

"We know your zip code is a far better predictor of your longevity than your genetic code," said Flower.

For a system built around these behaviors, team-based care and a standardization of protocols that end unneeded variation in care are crucial. Flower underscored the importance of disintermediation of the entire health system so that physicians won't have to go through health systems, payers, and employers to access their patients—and vice versa.

Employers have already started to play a more active role[1] in their employees' care, and this trend will continue in the coming decade, with employers looking to deal directly with physicians and penetrate through intermediaries. Flower gave the examples of Haven—the well-known joint venture[2] of Amazon, Berkshire Hathaway, and JP Morgan—and Walmart's continued efforts to get more involved in healthcare.

To sustain this environment, risk must be redistributed and moved away from fee for service and treat to code and toward "transparent and competitive payment models," such as bundled payment, said Flower. Payment elements of this changed care delivery environment include spot auctions, in which a patient can essentially shop their area for a service, see how much they would pay, read reviews of a provider, and make an appointment online. Flower compared it to booking a hotel or a seat on an airplane.

Lastly, complementing these behaviors, technology will fill gaps in the system. However, Flower emphasized, technology should never become a substitute for human contact. Instead, it should keep the patient directly hooked into the system and facilitate communication across the continuum. Recognizing that interoperability has not yet become a reality, Flower does see it becoming one in the coming decade.

Other elements include technologies like monitoring patches and smart drugs, which will be supported by blockchain, as well as elements the healthcare system has already started introducing into care delivery, such as artificial intelligence, big data, and personalized medicine that fits a patient's specific needs. ◆

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Digital Health Lessons From Around the World

ALTHOUGH NO SINGLE COUNTRY has perfected use of digital health, there are some takeaways from what countries around the world are doing successfully, according to John D. Halamka, MD, MS, chief information officer, Beth Israel Deaconess Health System, who presented at the Association of Community Cancer Centers' 45th Annual Meeting & Cancer Center Business Summit,

Halamka recently traveled to 14 countries in 60 days to learn how they are using technology in healthcare and gain insights from other societies. In China, families line up at 4 AM at academic medical centers to get treatment because they don't think the community is the place where they should get care and they don't have primary care doctors. According to Halamka, there is no order to the medical system, so President Xi Jinping came up with the idea of examining past experiences of patients to inform how patients should experience care in the future and using digital tools to tell patients where they should be getting care.

A pilot project is taking place throughout the city of Shanghai to design a common data set. The government is forcing every provider at every encounter to submit the data. "I'm not saying it's good, but it's efficient," Halamka said. The pilot gives China an opportunity to understand the care experience for 29 million citizens and use that to inform care in the future.

In India, patients own their data, so they can bring their medical records with them to any doctor they visit. The area Halamka visited was very poor, with an average daily income of $1.50, a lack of infrastructure, and a lack of medical care. However, the area had 4G cell phone service.

The Gates Foundation is trying to figure out a way to create a set of services accessible by cell phone so patients and families can input symptoms and find out where to go. Under the plan, every village would have a telemedicine liaison, where families can connect with an expert for a consultation for $1. And maybe, Halamka said, if a system like that can work in poor, rural areas of India, it can work in places such as Massachusetts.

"Sometimes, you actually have to experiment outside the United States to get it right," Halamka noted.

In the Nordic countries, the technology isn't the problem; the political circumstances are. Although these countries have decided healthcare for all is a right and that data will be shared across the community, they are now grappling with the General Data Protection Regulation. Norway wants to share genomic information, but how does that kind of information get deidentified?

Finland passed a law declaring that a person's deidentified medical record belongs to the public because society is keeping that person healthy. "So, how can you deprive society of your life experiences if it could help someone in the future?" Halamka asked.

There is no ability to opt out in Finland because it is the law, and Halamka marveled at trying to get something like this instituted in the United States, where each state has different privacy laws.

In Scotland, every citizen has a problem list, a medication list, last laboratory data, and allergy information in a common database that every emergency doctor in the country can access. "You show up in an emergency department, [and] we already know who you are; we already know what your problems are," Halamka said. "And we don't give you unnecessary, unsafe care."

However, with good ideas, sometimes it's better "to be a fast follower than an early adopter," Halamka said, using Australia as an example. Although the country had the good idea to make every medical record available to every patient in a single portal, it made a mistake with the data standard it chose: PDF. As a result, PDFs received by each doctor were making it difficult to perform tasks like drug–drug interaction checks.

In the United States there have been 800 pages of proposed rules to grant every patient full digital access to their clinical and financial data so they will be able to share that information at their will. So far, Halamka said, he is fairly happy with the suggestions that "will make patient care navigation easier for all."

Halamka was the second patient in the Human Genome Project, which means anyone can look up his genomic data. As someone who participated, he now knows that he has a high likelihood of dying from prostate cancer. Although there have been recommendations to stop prostate-specific antigen (PSA) testing because it is not effective in the overall population, Halamka is not the overall population. In contrast, he is a healthy individual who keeps to a vegan diet, and his cholesterol is low. As a result, it doesn't make sense to order a low-density lipoprotein cholesterol test for him every year, but it does make sense to order a PSA test every year.

A pilot project is taking place throughout the city of Shanghai to design a common data set. The government is forcing every provider at every encounter to submit the data. Said John D. Halamka, MD, MS, chief informtion officer, Beth Israel Deaconess Health System, "I'm not saying it's good, but it's efficient."

"That's the kind of care planning you'd like to develop," he said. But this depends on sharing data, and the country isn't quite sure how it feels about sharing these data yet.

The collection and use of data also enable the healthcare system to implement artificial intelligence and machine learning. There are some concerns about both because they are only as good as the data being used, and a lot of basic information being collected and input are flawed.

"This is not about replacing doctors," Halamka said. "It's about giving doctors the tools to allow them to practice more efficiently and safely." ◆

COA Close to Filing OCM 2.0 for Federal Review

AFTER A YEAR IN DEVELOPMENT, the Community Oncology Alliance (COA) will file its alternative to CMS' Oncology Care Model (OCM) sometime in April 2019 with the Physician-Focused Payment Model Technical Advisory Committee (PTAC), a federal agency that reviews models for possible use by Medicare.

Bo Gamble, COA's director of strategic practice initiatives, announced during a panel at the 2019 Community Oncology Conference, held in Orlando, Florida, that the plan known as OCM 2.0 was near completion. Gamble appeared with Basit Chaudhry, MD, PhD, founder and chief executive officer of Tuple Health; Kavita Patel, MD, MS, a former Obama administration policy official also with Tuple Health; and Bruce Gould, MD, medical director of Northwest Georgia Oncology Centers and chair of COA's committee on oncology payment reform.

Gamble, Patel, and Gould previously reported on OCM 2.0 during COA's Payer Exchange Summit in October 2018, describing it as a template that could be used by Medicare, commercial payers, and even self-insured employers, by addressing many of the frustrations that community oncology practices see with the current incarnation of OCM. These include issues with patient attribution, a high number of reporting burdens, methodological flaws in the rating

of geography and quality measures, and a reimbursement scheme that has not kept pace with the soaring cost of oncology therapies. Most of all, as COA expressed a year ago, a lack of transparency[1] makes it difficult for participants to understand results for their practices.

The session, "From OCM 1.0 to 2.0: Two Paths to Payment Reform," offered an additional update on the complexities of CMS' signature 5-year alternative payment model (APM), which covers 176 practices and is scheduled to run through June 2021. So far, no plan for an OCM extension or successor has been announced, and Gamble said after the session that practices need information on what will come next.

The Community Oncology Alliance decided to work with its member practices, some payers, and pharmaceutical companies to develop OCM 2.0 simply because the errors and problems it identified were not being fixed quickly, and the escalating costs of oncology drugs in Medicare Part D were not getting enough attention.

Chaudhry explained that the OCM has reached a crossroads. Early on in the model, practices often focused on implementing administrative requirements. As a result, more substantive clinical transformation efforts frequently started later. Results from performance period 3, which were released a few weeks ago, did not show progressive improvement overall. The share of practices that received a performance-based payment in performance period 3 was the same as that in performance period 2. The percentage of practices achieving shared savings did not increase.

With OCM practices facing a deadline to decide whether they will take on 2-sided risk, Chaudhry said, "both of these trends are quite concerning."

Gamble and Gould said there are many things about the OCM that have improved cancer care, but the way the model handles drug pricing means that practices that are doing everything right can still miss out on shared savings.

"I'm a big believer in personal responsibility," Gould said. Oncology practices should be good stewards of healthcare dollars; they must provide team-based care that helps patients navigate their way through cancer treatment, including "closing the loop" after a consultation.

But, Gould added, the OCM uses pricing models that were developed with claims data from 2012 to 2015, before the explosion of immuno-oncology drugs. Not only do newer drugs cost more per month, but patients take today's targeted therapies for longer periods of time. Even with OCM changes like the novel therapy adjustment and the trend factor, Gould said, "[the] pricing model is not relevant with what we do today."

The complexity of the model also strains practices, Gould said, estimating that a practice with 1000 patients will need to report 8000 to 15,000 data elements, many of them by hand.

When an audience member noted that the OCM doesn't account for off-label uses that appear in the National Comprehensive Cancer Network guidelines, Patel said it would be unthinkable for a government agency like the Center for Medicare & Medicaid Innovation (CMMI) to look beyond FDA-approved uses in building a reimbursement model. It's just not how the government operates, she said.

Patel said that instead of trying to stay ahead of rising drug prices with "complex and wrong adjustment factors," CMMI would be better off coming up with a set price for what it costs to treat a patient "and give you something on top of that so you can survive and thrive.

"But I'm not in charge of CMS, so it's easy for me to say that," she added.

During his presentation, Gamble reviewed the process that COA used to develop the proposal that will go to PTAC, which was created to evaluate APMs developed by physicians in addition to those developed by CMMI. Despite expectations early in the Trump administration that PTAC's profile would increase, so far CMS has not authorized oncology models blessed by the group to compete with the OCM.

COA decided to work with its member practices, some payers, and pharmaceutical companies to develop OCM 2.0 simply because the errors and problems it identified were not being fixed quickly and the escalating costs of oncology drugs in Medicare Part D were not getting enough attention. In short, Gamble said, the alliance asked, "Why is there not a better way to do this?"

As Gould's committee collected feedback, Gamble said, a key step involved gathering practice leaders responsible for understanding the revenue cycle of the OCM and bringing them together to brainstorm solutions. Another critical step was meeting directly with leaders of drug companies and asking how COA could forge value-based agreements directly with providers—something that payers typically do with pharmaceutical companies while purposely leaving providers in the dark. "That lack of transparency is impacting the patient and the provider teams," Gamble said.

"We had a series of close to 12 face-to-face discussions with drug companies," Gamble noted. The tone was, "We see the challenges in your world, you see the challenges in our world," he added.

OCM 2.0 will not look like other payment models, Gamble said. It will be more of framework based on the best elements seen by other oncology models, including initiatives from the American Society of Clinical Oncology. But Gamble promised it will take on the issue of rising drug costs in ways other models have not.

Meetings with pharmaceutical companies in particular will soon bear fruit, Gamble added. "I believe in a very short while, you're going to see more value-based scenarios involving providers than you ever have before," he said. ◆

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Step Therapy in Medicare Advantage Hurts Patients, Providers, Says Schwartzberg

STEP THERAPY, WHICH REQUIRES that patients try the payer's preferred treatment before the one a physician recommends, is harmful to both sides of the doctor–patient relationship, according to Lee B. Schwartzberg, MD, executive director of the West Cancer Center and Research Institute, who spoke on April 5, 2019, at the Community Oncology Conference in Orlando, Florida.

Schwartzberg, who also recently became chief medical officer for OneOncology, a national partnership of community oncologists,[1] discussed the challenges of step therapy with Ted Okon, MBA, executive director of the Community Oncology Alliance (COA).

Okon and COA were among the first to criticize the August 2018 directive from HHS to allow Medicare Advantage plans to include step therapy as a cost-saving measure, calling it a "fail first" strategy.[2,3]

During open enrollment last fall, several national insurers declined to say whether they were pursuing step therapy, and if seniors selected plans based on price, they might not know whether their plan featured this provision until after they had received a cancer diagnosis. A report from Deft Research found that the Medicare switch rate increased from 11% in 2018 to 14% in 2019, and UnitedHealthcare's share of the Medicare Advantage market is now up to 25%, and Humana has 17%.[4]

"When it comes to step therapy, there are so many problems, it's remarkable we stand for it," Schwartzberg said. The practice, seen for years in conditions like diabetes, is questionable when treating a chronic disease, Schwartzberg said, but in oncology it's particularly alarming. Patients with cancer often do not have the luxury to wait for a therapy to fail before moving to the one a physician preferred in the first place, he said.

It's reasonable to assume that payers use step therapy to force patients to start with older, cheaper drugs or generics, but that's not always true. The first drug a patient tries "could be the one that's the most profitable," Okon said. At least 19 states have passed laws to curb step therapy, and more states are considering legislation, he said.

Schwartzberg said in some cases, step therapy is applied for supportive drugs, but in others, it is used for therapeutic drugs. "This is antithetical to precision medicine," he said.

He offered an example in which a patient was pushed to try a different drug even though the patient's serum creatinine levels were already elevated and the substitute would increase them. Pharmacy benefit managers "take a very narrow view of what the 'cost' is," Schwartzberg said. "They don't take into account the patient experience at all."

Another example includes different choices for filgrastim. Schwartzberg said he's all for using biosimilars when they are indicated, but he has some patients who live far from his clinic, and each visit is 100 miles round trip for the patient and the caregiver. Some forms of filgrastim come in a prefilled, subcutaneous injection that the patient or caregiver can administer, but other forms do not.

Another challenge is in variation among payers. Schwartzberg presented a slide showing different policies for denosumab, a subcutaneous injection used to treat bone problems in patients with cancer, including those with solid tumors and multiple myeloma. He compared policies for Humana, the Blues, Cigna, Aetna, and UnitedHealthcare. Among the group, Aetna had the most expansive policy.

Humana requires patients with multiple myeloma and those with solid tumors to try other drugs first but exempts patients with prostate cancer from this requirement, Schwartzberg said. According to the information he presented, UnitedHealthcare also requires patients to try an intravenous bisphosphonate, and once on denosumab, they can take it for only 12 months.

Schwartzberg said knowing what company name is on the insurance card doesn't tell him much because not all Medicare Advantage plans have step therapy, and typically patients have no idea their plans allow this. It's not uncommon for his office to get an urgent phone call from a pharmacy saying the health plan will not cover the therapy that Schwartzberg has carefully selected and discussed with the patient. He must default to what the plan allows.

This does not help build trust with patients, he said. "It's so stress provoking for patients. They say, 'You prescribed this. Now they are telling me this.'"

Schwartzberg said patients get what's going on, and he won't lie to them. "I tell them, 'That's not the drug that I would use, but we'll try it.'"

Okon urged the oncologists in the audience to contact state and federal legislators on this issue. "There are a lot of members of Congress who understand this, and they are very against it," he said. ◆

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"Whatever's next, I want to be all in."

CYRAMZA boosted efficacy results vs docetaxel alone in the REVEL ITT population—**with consistent results in patients with rapidly progressing disease***[1]

Exploratory Subgroup Analysis: Patients With Rapidly Progressing Disease* (n=209)[1]

Time-to-progression ≤12 weeks

OS†[1] (95% CI)

CYRAMZA + docetaxel		Placebo + docetaxel
9.1 MONTHS‡	vs	5.8 MONTHS‡
(6.7, 10.8)		(4.3, 7.5)

Unstratified HR=0.74 (95% CI: 0.54, 1.00)

ORR[1] (95% CI)

CYRAMZA + docetaxel		Placebo + docetaxel
19%	vs	9%
(12, 28)		(4, 17)

PFS§[1] (95% CI)

CYRAMZA + docetaxel		Placebo + docetaxel
3.6 MONTHS‡	vs	1.6 MONTHS‡
(2.8, 4.2)		(1.5, 2.6)

Unstratified HR=0.73 (95% CI: 0.55, 0.97)

REVEL EXPLORATORY ANALYSIS The REVEL trial was not adequately powered, nor error-controlled, for subgroup analysis. Treatment differences observed in this subgroup cannot be regarded as statistically significant. The analysis described here was post hoc and exploratory.[2]

REVEL ITT Population (n=1253)[3]

OS‖[3] Major Outcome Measure (95% CI)

CYRAMZA + docetaxel		Placebo + docetaxel
10.5 MONTHS‡	vs	9.1 MONTHS‡
(9.5, 11.2)		(8.4, 10.0)

HR=0.86 (95% CI: 0.75, 0.98) *P*=0.024

ORR¶[3] Supportive Outcome Measure (95% CI)

CYRAMZA + docetaxel		Placebo + docetaxel
23%	vs	14%
(20, 26)		(11, 17)

P<0.001

PFS#[3] Supportive Outcome Measure (95% CI)

CYRAMZA + docetaxel		Placebo + docetaxel
4.5 MONTHS‡	vs	3.0 MONTHS‡
(4.2, 5.4)		(2.8, 3.9)

HR=0.76 (95% CI: 0.68, 0.86) *P*<0.001

STUDY DESIGN The phase III REVEL trial evaluated the efficacy and safety of CYRAMZA plus docetaxel vs placebo plus docetaxel in patients with mNSCLC with disease progression on or after platinum-based chemotherapy. Major efficacy outcome measure was OS. Supportive efficacy outcome measures were PFS and ORR. All patients were required to have ECOG PS 0 or 1. Patients were randomized 1:1 to receive either CYRAMZA 10 mg/kg (n=628) or placebo (n=625), in combination with docetaxel at 75 mg/m^2 every 21 days.[3]

*Rapidly progressing disease is defined by time-to-progression **within 9 or 12 weeks after starting initial platinum-based treatment.**[4]

†The percentage of deaths at the time of analysis in the CYRAMZA plus docetaxel arm was 75.7% (84 patients) and 80.6% (79 patients) in the placebo plus docetaxel arm.

‡Median.

§The percentage of events at the time of analysis in the CYRAMZA plus docetaxel arm was 91% (101 patients) and 92.9% (91 patients) in the placebo plus docetaxel arm.

‖The percentage of deaths at the time of analysis was 68% (428 patients) and 73% (456 patients) in the CYRAMZA plus docetaxel and placebo plus docetaxel arms, respectively.

¶Disease progression and tumor response were assessed by investigators in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[5]

#The percentage of events at the time of analysis was 89% (558 patients) and 93% (583 patients) in the CYRAMZA plus docetaxel and placebo plus docetaxel arms, respectively.

ORR=complete + partial response; does not include stable disease.

CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; ITT=intent-to-treat; mNSCLC=metastatic non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PS=performance status.

INDICATION

CYRAMZA, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

IMPORTANT SAFETY INFORMATION FOR CYRAMZA

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

IMPORTANT SAFETY INFORMATION FOR CYRAMZA (CONT'D)

Warnings and Precautions

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In study 3, which evaluated CYRAMZA plus docetaxel in metastatic non-small cell lung cancer (NSCLC), the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDs or other antiplatelet therapy other than once-daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from study 3; therefore, the risk of pulmonary hemorrhage in these groups of patients is unknown. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, ATEs including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA plus docetaxel (6%) as compared to placebo plus docetaxel (2%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions (IRRs)

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, IRRs occurred in 6 out of 37 patients (16%), including 2 severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for grade 3 or 4 IRRs.

Gastrointestinal Perforations

- CYRAMZA is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. In study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel versus 0.3% for placebo plus docetaxel. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. CYRAMZA has not been studied in patients with serious or nonhealing wounds. CYRAMZA, as an antiangiogenic therapy, has the potential to adversely affect wound healing. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery. Resume CYRAMZA following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.

Clinical Deterioration in Child-Pugh B or C Cirrhosis

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- RPLS has been reported at a rate of <0.1% in clinical studies with CYRAMZA. Confirm the diagnosis of RPLS with MRI and discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome

- Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are ≥2 g over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to <2 g over 24 hours. Permanently discontinue CYRAMZA for urine protein levels >3 g over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction

- Monitor thyroid function during treatment with CYRAMZA.

Embryofetal Toxicity

- Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

Most Common Adverse Reactions

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus docetaxel and ≥2% higher than placebo plus docetaxel in study 3 were neutropenia (55% vs 46%; 49% vs 40%), fatigue/asthenia (55% vs 50%; 14% vs 11%), stomatitis/mucosal inflammation (37% vs 19%; 7% vs 2%), epistaxis (19% vs 7%; <1% vs <1%), febrile neutropenia (16% vs 10%; 16% vs 10%), peripheral edema (16% vs 9%; 0% vs <1%), thrombocytopenia (13% vs 5%; 3% vs <1%), lacrimation increased (13% vs 5%; <1% vs 0%), and hypertension (11% vs 5%; 6% vs 2%).
- The most common serious adverse events with CYRAMZA plus docetaxel in study 3 were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel.
- In patients ≥65 years of age, there were 18 (8%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 9 (4%) deaths for placebo plus docetaxel. In patients <65 years of age, there were 13 (3%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 26 (6%) deaths for placebo plus docetaxel.
- Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel-treated patients (9%) than in placebo plus docetaxel-treated patients (5%). The most common adverse events leading to treatment discontinuation of CYRAMZA were infusion-related reaction (0.5%) and epistaxis (0.3%).
- For patients with nonsquamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of grade ≥3 pulmonary hemorrhage was 1% for CYRAMZA plus docetaxel compared to 6% overall incidence and 1% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of grade ≥3 pulmonary hemorrhage was 2% for CYRAMZA plus docetaxel compared to 12% overall incidence and 2% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA plus docetaxel-treated patients in study 3 were hyponatremia (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (3.3% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

Drug Interactions

- No pharmacokinetic interactions were observed between ramucirumab and docetaxel.

Use in Specific Populations

- Pregnancy: Based on its mechanism of action, CYRAMZA can cause fetal harm. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no available data on CYRAMZA use in pregnant women to inform any drug-associated risks. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to newborn and infant development, and to use effective contraception during CYRAMZA therapy and for at least 3 months following the last dose of CYRAMZA.
- Lactation: Because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, advise women that breastfeeding is not recommended during treatment with CYRAMZA.
- Females of Reproductive Potential: Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Please see Brief Summary of Prescribing Information for CYRAMZA, including Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing, on adjacent pages.

RB-L HCP ISI 17SEP2015

Visit **CYRAMZAhcp.com** to find out more

References: 1. Data on file. Eli Lilly and Company. ONC20170503d. **2.** Data on file. Eli Lilly and Company. ONC20170503c. **3.** CYRAMZA (ramucirumab) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2017. **4.** Data on file. Eli Lilly and Company. ONC20170503a. **5.** Garon EB, Ciuleanu T-E, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384(9944):665-673.

CYRAMZA®
ramucirumab injection
10 mg/mL solution

CYRAMZA® (ramucirumab) injection
BRIEF SUMMARY: For complete safety, please consult the full Prescribing Information.

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

INDICATIONS AND USAGE
Non-Small Cell Lung Cancer:
CYRAMZA, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Hemorrhage
CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In Study 1, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In Study 2, the incidence of severe bleeding was 4.3% for CYRAMZA plus paclitaxel and 2.4% for placebo plus paclitaxel. Patients with gastric cancer receiving nonsteroid anti-inflammatory drugs (NSAIDs) were excluded from enrollment in Studies 1 and 2; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. In Study 3, the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDS or other antiplatelet therapy other than once daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from Study 3; therefore the risk of pulmonary hemorrhage in these groups of patients is unknown. In Study 4, the incidence of severe bleeding was 2.5% for CYRAMZA plus FOLFIRI and 1.7% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience severe bleeding.
Arterial Thromboembolic Events
Serious, sometimes fatal, arterial thromboembolic events (ATEs) including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials including 1.7% of 236 patients who received CYRAMZA as a single agent for gastric cancer in Study 1. Permanently discontinue CYRAMZA in patients who experience a severe ATE.
Hypertension
An increased incidence of severe hypertension occurred in patients receiving CYRAMZA as a single agent (8%) as compared to placebo (3%) and in patients receiving CYRAMZA plus paclitaxel (15%) as compared to placebo plus paclitaxel (3%), in patients receiving CYRAMZA plus docetaxel (6%) as compared to placebo plus docetaxel (2%), and in patients receiving CYRAMZA plus FOLFIRI (11%) as compared to placebo plus FOLFIRI (3%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.
Infusion-Related Reactions
Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, infusion-related reactions (IRRs) occurred in 6 out of 37 patients (16%), including two severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for Grade 3 or 4 IRRs.
Gastrointestinal Perforations
CYRAMZA is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. Four of 570 patients (0.7%) who received CYRAMZA as a single agent in clinical trials experienced gastrointestinal perforation. In Study 2, the incidence of gastrointestinal perforations was also increased in patients that received CYRAMZA plus paclitaxel (1.2%) as compared to patients receiving placebo plus paclitaxel (0.3%). In Study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel and 0.3% for placebo plus docetaxel. In Study 4, the incidence of gastrointestinal perforation was 1.7% for CYRAMZA plus FOLFIRI and 0.6% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.
Impaired Wound Healing
Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. CYRAMZA has not been studied in patients with serious or non-healing wounds. CYRAMZA, as an antiangiogenic therapy, has the potential to adversely affect wound healing. Withhold CYRAMZA prior to surgery. Resume following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.
Clinical Deterioration in Patients with Child-Pugh B or C Cirrhosis
Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
RPLS has been reported with a rate of <0.1% in clinical studies with CYRAMZA. Confirm the diagnosis of RPLS with MRI and discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.
Proteinuria Including Nephrotic Syndrome
In Study 4, severe proteinuria occurred more frequently in patients treated with CYRAMZA plus FOLFIRI compared to patients receiving placebo plus FOLFIRI. Severe proteinuria was reported in 3% of patients treated with CYRAMZA plus FOLFIRI (including 3 cases [0.6%] of nephrotic syndrome) compared to 0.2% of patients treated with placebo plus FOLFIRI. Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are 2 or more grams over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to less than 2 grams over 24 hours. Permanently discontinue CYRAMZA for urine protein levels greater than 3 grams over 24 hours or in the setting of nephrotic syndrome.
Thyroid Dysfunction
Monitor thyroid function during treatment with CYRAMZA. In Study 4, the incidence of hypothyroidism reported as an adverse event was 2.6% in the CYRAMZA plus FOLFIRI treated patients and 0.9% in the placebo plus FOLFIRI treated patients.
Embryofetal Toxicity
Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
CYRAMZA Administered in Combination with Docetaxel
Study 3 was a multinational, randomized, double-blind study conducted in patients with NSCLC with disease progression on or after one platinum-based therapy for locally advanced or metastatic disease. Patients received either CYRAMZA 10 mg/kg intravenously plus docetaxel 75 mg/m^2 intravenously every 3 weeks or placebo plus docetaxel 75 mg/m^2 intravenously every 3 weeks. Due to an increased incidence of neutropenia and febrile neutropenia in patients enrolled in East Asian sites, Study 3 was amended and 24 patients (11 CYRAMZA plus docetaxel, 13 placebo plus docetaxel) at East Asian sites received a starting dose of docetaxel at 60 mg/m^2 every 3 weeks. Study 3 excluded patients with an ECOG PS of 2 or greater, bilirubin greater than the upper limit of normal (ULN), uncontrolled hypertension, major surgery within 28 days, radiographic evidence of major airway or blood vessel invasion by cancer, radiographic evidence of intra-tumor cavitation, or gross hemoptysis within the preceding 2 months, and patients receiving therapeutic anticoagulation or chronic anti-platelet therapy other than once daily aspirin. The study also excluded patients whose only prior treatment for advanced NSCLC was a tyrosine kinase (epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK]) inhibitor. The data described below reflect exposure to CYRAMZA plus docetaxel in 627 patients in Study 3. Demographics and baseline characteristics were similar between treatment arms. Median age was 62 years; 67% of patients were men; 84% were White and 12% were Asian; 33% had ECOG PS 0; 74% had non-squamous histology and 25% had squamous histology. Patients received a median of 4.5 doses of CYRAMZA; the median duration of exposure was 3.5 months, and 195 (31% of 627) patients received CYRAMZA for at least six months. In Study 3, the most common adverse reactions (all grades) observed in CYRAMZA plus docetaxel-treated patients at a rate of ≥30% and ≥2% higher than placebo plus docetaxel were neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation. Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel-treated patients (9%) than in placebo plus docetaxel-treated patients (5%). The most common adverse events leading to treatment discontinuation of CYRAMZA were infusion-related reaction (0.5%) and epistaxis (0.3%). For patients with non-squamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of ≥Grade 3 pulmonary hemorrhage was 1% for CYRAMZA plus docetaxel compared to 6% overall incidence and 1% for ≥Grade 3 pulmonary hemorrhage for placebo plus docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of ≥Grade 3 pulmonary hemorrhage was 2% for CYRAMZA plus docetaxel compared to 12% overall incidence and 2% for ≥Grade 3 pulmonary hemorrhage for placebo plus docetaxel. The most common serious adverse events with CYRAMZA plus docetaxel were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel. In patients ≥65 years, there were 18 (8%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 9 (4%) deaths for placebo plus docetaxel. In patients <65 years, there were 13 (3%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 26 (6%) deaths for placebo plus docetaxel. Table 4 provides the frequency and severity of adverse reactions in Study 3.

Table 4: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA in Study 3

Adverse Reactions (MedDRA) System Organ Class	CYRAMZA plus docetaxel (N=627)		Placebo plus docetaxel (N=618)	
	All Grades (Frequency %)	Grade 3-4 (Frequency %)	All Grades (Frequency %)	Grade 3-4 (Frequency %)
Blood and Lymphatic System Disorders				
Febrile neutropenia	16	16	10	10
Neutropenia	55	49	46	40
Thrombocytopenia	13	3	5	<1
Gastrointestinal Disorders				
Stomatitis/Mucosal inflammation	37	7	19	2
Eye Disorders				
Lacrimation increased	13	<1	5	0
General Disorders and Administration Site Disorders				
Fatigue/Asthenia	55	14	50	11
Peripheral edema	16	0	9	<1
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	19	<1	7	<1
Vascular Disorders				
Hypertension	11	6	5	2

Clinically relevant adverse drug reactions reported in ≥1% and <5% of the CYRAMZA plus docetaxel-treated patients in Study 3 were hyponatremia (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (3.3% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).
Immunogenicity
As with all therapeutic proteins, there is the potential for immunogenicity. In 23 clinical trials, 86/2890 (3.0%) of CYRAMZA-treated patients tested positive for treatment-emergent anti-ramucirumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in 14 of the 86 patients who tested positive for treatment-emergent anti-ramucirumab antibodies.
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 incidence of antibodies to CYRAMZA with the incidences of antibodies to other products may be misleading.

DRUG INTERACTIONS
No pharmacokinetic (PK) interactions were observed between ramucirumab and docetaxel.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
Based on its mechanism of action, CYRAMZA can cause fetal harm. Animal models link angiogenesis, VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no available data on CYRAMZA in pregnant women to inform any drug-associated risks. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. The background risk of major birth defects and miscarriage for the indicated populations are 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. Advise pregnant women of the potential risk to a fetus.
Animal Data
No animal studies have been specifically conducted to evaluate the effect of ramucirumab on reproduction and fetal development. In mice, loss of the VEGFR2 gene resulted in embryofetal death and these fetuses lacked organized blood vessels and blood islands in the yolk sac. In other models, VEGFR2 signaling was associated with development and maintenance of endometrial and placental vascular function, successful blastocyst implantation, maternal and feto-placental vascular differentiation, and development during early pregnancy in rodents and non-human primates. Disruption of VEGF signaling has also been associated with developmental anomalies including poor development of the cranial region, forelimbs, forebrain, heart, and blood vessels.

CYRAMZA® (ramucirumab) injection RB-L HCP BS 27MAR2017

Lactation

Risk Summary

There is no information on the presence of ramucirumab in human milk, the effects on the breast-fed infant, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, advise women that breastfeeding is not recommended during treatment with CYRAMZA.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action, CYRAMZA can cause fetal harm. Advise females of reproductive potential to use effective contraception while receiving CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

Infertility

Females

Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Pediatric Use

The safety and effectiveness of CYRAMZA in pediatric patients have not been established. In animal studies, effects on epiphyseal growth plates were identified. In cynomolgus monkeys, anatomical pathology revealed adverse effects on the epiphyseal growth plate (thickening and osteochondropathy) at all doses tested (5-50 mg/kg). Ramucirumab exposure at the lowest weekly dose tested in the cynomolgus monkey was 0.2 times the exposure in humans at the recommended dose of ramucirumab as a single agent.

Geriatric Use

Of the 563 CYRAMZA-treated patients in two randomized gastric cancer clinical studies, 36% were 65 and over, while 7% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Of the 1253 patients in Study 3, 455 (36%) were 65 and over and 84 (7%) were 75 and over. Of the 627 patients who received CYRAMZA plus docetaxel in Study 3, 237 (38%) were 65 and over, while 45 (7%) were 75 and over. In an exploratory subgroup analysis of Study 3, the hazard ratio for overall survival in patients less than 65 years old was 0.74 (95% CI: 0.62, 0.87) and in patients 65 years or older was 1.10 (95% CI: 0.89, 1.36).

Renal Impairment

No dose adjustment is recommended for patients with renal impairment based on population pharmacokinetic analysis.

Hepatic Impairment

No dose adjustment is recommended for patients with mild (total bilirubin within upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN, or total bilirubin >1.0-1.5 times ULN and any AST) or moderate (total bilirubin >1.5-3.0 times ULN and any AST) hepatic impairment based on population pharmacokinetic analysis. Clinical deterioration was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA.

DOSAGE AND ADMINISTRATION

Do not administer CYRAMZA as an intravenous push or bolus.

Recommended Dose and Schedule

The recommended dose of CYRAMZA is 10 mg/kg administered by intravenous infusion over 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion. Continue CYRAMZA until disease progression or unacceptable toxicity.

Premedication

Prior to each CYRAMZA infusion, premedicate all patients with an intravenous histamine H_1 antagonist (e.g., diphenhydramine hydrochloride). For patients who have experienced a Grade 1 or 2 infusion reaction, also premedicate with dexamethasone (or equivalent) and acetaminophen prior to each CYRAMZA infusion.

Dose Modifications

Infusion-Related Reactions (IRR)

- Reduce the infusion rate of CYRAMZA by 50% for Grade 1 or 2 IRRs.
- Permanently discontinue CYRAMZA for Grade 3 or 4 IRRs.

Hypertension

- Interrupt CYRAMZA for severe hypertension until controlled with medical management.
- Permanently discontinue CYRAMZA for severe hypertension that cannot be controlled with antihypertensive therapy.

Proteinuria

- Interrupt CYRAMZA for urine protein levels ≥2 g/24 hours. Reinitiate treatment at a reduced dose of 8 mg/kg every 3 weeks once the urine protein level returns to <2 g/24 hours. If the protein level ≥2 g/24 hours reoccurs, interrupt CYRAMZA and reduce the dose to 6 mg/kg every 3 weeks once the urine protein level returns to <2 g/24 hours.
- Permanently discontinue CYRAMZA for urine protein level >3 g/24 hours or in the setting of nephrotic syndrome.

Wound Healing Complications

- Interrupt CYRAMZA prior to scheduled surgery until the wound is fully healed.

Arterial Thromboembolic Events, Gastrointestinal Perforation, or Grade 3 or 4 Bleeding

- Permanently discontinue CYRAMZA.

For toxicities related to docetaxel, refer to the current respective prescribing information.

PATIENT COUNSELING INFORMATION

- **Hemorrhage:**

Advise patients that CYRAMZA can cause severe bleeding. Advise patients to contact their health care provider for bleeding or symptoms of bleeding including lightheadedness.

- **Arterial thromboembolic events:**

Advise patients of an increased risk of an arterial thromboembolic event.

- **Hypertension:**

Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if symptoms from hypertension occur including severe headache, lightheadedness, or neurologic symptoms.

- **Gastrointestinal perforations:**

Advise patients to notify their health care provider for severe diarrhea, vomiting, or severe abdominal pain.

- **Impaired wound healing:**

Advise patients that CYRAMZA has the potential to impair wound healing. Instruct patients not to undergo surgery without first discussing this potential risk with their health care provider.

- **Pregnancy and fetal harm:**

Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to postnatal newborn and infant development and to use effective contraception during CYRAMZA therapy and for at least 3 months following the last dose of CYRAMZA.

- **Lactation:**

Advise patients not to breastfeed during CYRAMZA treatment.

- **Infertility:**

Advise females of reproductive potential regarding potential infertility effects of CYRAMZA.

Additional information can be found at www.CYRAMZAhcp.com.

Lilly

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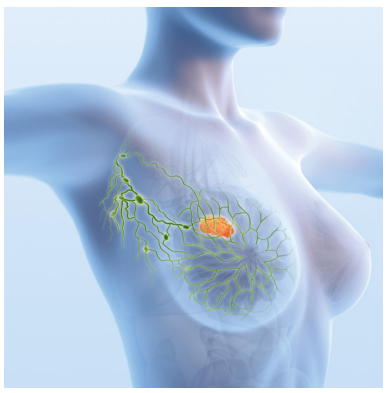
Coverage by Mary Caffrey, Allison Inserro, Jaime Rosenberg, Samantha DiGrande, and Wallace Stephens

FDA Approves Atezolizumab Combination for Triple-Negative Breast Cancer

THE FDA HAS GRANTED accelerated approval[1] for atezolizumab (Tecentriq) in combination with nab-paclitaxel (Abraxane) for the treatment of adults with unresectable locally advanced or metastatic triple-negative breast cancer—a form of breast cancer with few treatment options—whose tumors express the marker programmed death ligand-1 (PD-L1). The combination is the first approved immunotherapy regimen for breast cancer.

The agency also approved the VENTANA PD-L1 assay as the first companion diagnostic for identifying which patients should receive the atezolizumab combination.



The approval was based on progression-free survival (PFS) data from the phase 3 IMpassion130 study, which demonstrated that among 902 patients who had not received previous chemotherapy for metastatic disease, the combination reduced the risk of disease worsening or death by 40%.

"The Tecentriq regimen is an exciting new treatment for certain people living with metastatic triple-negative breast cancer, a difficult-to-treat disease," said Hayley Dinerman, JD, executive director, Triple Negative Breast Cancer Foundation, in a statement.[2] "Chemotherapy alone has been the mainstay of treatment for many years, so it's encouraging to now have an immunotherapy combination available for people with PD-L1–positive disease."

During the study, patients were randomized to receive either atezolizumab 840 mg or placebo on days 1 and 15 of every 28-day cycle, plus nab-paclitaxel 100 mg/m^2 on days 1, 8, and 15 of every 28-day cycle. For patients treated with the atezolizumab combination, median PFS was 7.2 months, compared with a median PFS of 5.5 months among patients receiving chemotherapy alone. Among patients expressing PD-L1, median PFS was 7.4 months for patients receiving the atezolizumab combination and 4.8 months for patients receiving chemotherapy alone.

The objective response rate (ORR) among patients receiving the atezolizumab combination was 53% while ORR among patients receiving chemotherapy alone was 33%. While overall survival data are immature, an interim analysis[3] showed that median overall survival was 25 months and 15.5 months, respectively.

Throughout the study, the most common grade 3 or 4 adverse effects included neutropenia, tingling or numbness in the hands and feet, low blood potassium level, pneumonia, and low red blood cell count.

According to the FDA, continued approval of this combination in this treatment setting is contingent upon a confirmatory trial.

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Biologic Age Associated With Breast Cancer Risk

SCIENTISTS AT THE NATIONAL Institutes of Health have recently found that biologic age, or a DNA-based estimate of a person's age, is associated with future development of breast cancer.

A person's age is among the "strongest predictions of cancer, chronic disease, and mortality, but biologic responses to aging differ among people," wrote the study authors. Investigators measured baseline blood DNA methylation of 2764 women enrolled in the study[1] who were cancer-free at the time of blood collection and all sisters of women with previously diagnosed breast cancer. The researchers found that 1566 subsequently developed breast cancer after an average time frame of 6 years.

Biological age acceleration was defined for each woman by comparing her estimated biological age with her chronological age. The authors utilized 3 methylation-based "clocks" previously developed by other researchers to determine the biological age acceleration for each participant. The clocks work by measuring methylation found at specific locations within DNA. The study demonstrated that for every 5 years that a woman's biologic age was older than her chronologic age, she had a 15% increase in her chance of developing breast cancer.

"We found that if your biologic age is older than your chronologic age, your breast cancer risk is increased. The converse was also true. If your biologic age is younger than your chronologic age, you may have decreased risk of developing breast cancer," said Jack Taylor, MD, PhD, head of the National Institute of Environmental Health Sciences Molecular and Genetic Epidemiology Group and corresponding author of the study, in a press release.[2]

The study was able to conclude that using DNA methylation to measure biologic age may help future researchers better understand and identify specific patients at risk of developing cancer and other age-related diseases. The research team plans to continue using epigenetic data, as well as information on genetics, environment, and lifestyle factors, to better understand how they contribute to disease risks.

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Breast Surgeons Seek Genetic Testing for All Patients With Breast Cancer

NEW GUIDELINES ISSUED[1] IN February from the American Society of Breast Surgeons (ASBrS) called for giving every person diagnosed with breast cancer a genetic test with a multigene panel. The consensus statement was approved by the society's board of directors and has 5 elements:

1. Breast surgeons, genetic counselors, and other knowledgeable professionals can provide education and counseling and make recommendations and arrange testing.

2. Genetic testing should be available to all patients with a personal history of breast cancer. Testing should include *BRCA1/2*, *PALB2*, and other genes appropriate with family history.

3. Patients who had genetic testing may benefit from updated testing. The guidelines update scenarios for patients to have updated testing if initial testing was done prior to 2014.

4. Genetic testing should be made available to those without a history of breastcancer who meet guidelines of the National Comprehensive Cancer Network (NCCN). Sometimes this occurs if an affected relative cannot be tested.

5. Variants of uncertain significance are DNA sequences that are not clinically actionable. This type of result must be considered inconclusive.

The update follows a study published in 2018 in the *Journal of Clinical Investigation*, the official publication of the American Society of Clinical Oncology, which called for all patients with a breast cancer diagnosis to undergo expanded panel testing. Researchers reviewing registry from 959 patients found that patients with breast cancer who met NCCN testing criteria had similar rates of pathogenic or likely pathogenic hereditary mutations (9%) as those who did not meet the NCCN criteria (8%).[2]

"I am excited by our new guidelines and look forward to the day NCCN updates its guidelines, also. The exciting new data demonstrated that about half of patients with breast cancer have clinically actionable mutations that are being missed when genetic testing is restricted to patients meeting current NCCN guidelines," Walton Taylor, MD, president of American Society of Breast Surgeons, said in a statement to the society membership. "As genetic testing expands, it is important to choose the lab carefully, making sure they provide quality testing with accurate results and appropriate follow-up."

In their consensus statement, panel members stated that about 10% of the 266,000 new cases of invasive breast cancer in the United States each year would be linked to a pathogenic germline variant of one of several genes; more than 50% of these are mutations of *BRCA1/2*. While testing costs less than it once did and fewer barriers exist, some remain—among them, the limited number of genetic counselors who can meet with patients and family members.

Genetic counselors[3] play a critical role, because they are needed to help patients and family members interpret results. Some health insurers,[4] including Cigna, require their assistance to accompany testing. Awareness about *BRCA1/2* mutations soared in 2013 after actress Angelina Jolie disclosed her decision to have a double mastectomy[5] due to her own family history. As a result, many payers took a cautious view, wary that the fear of breast cancer would cause some women to have surgery they did not need.

In their consensus statement, the ASBrS said that surgeons can inform patients of the risks and benefits of testing and discuss risk management strategies for patients who test positive.

At least 1 genetic provider praised the new guidelines. "We applaud the ASBrS for recognizing the important advances in scientific knowledge, and for recommending genetic testing for all people with breast cancer," said Johnathan Lancaster, MD, PhD, chief medical officer for Myriad Genetics. "The valuable information provided by genetic testing enhances physicians' ability to select appropriate precision treatments, personalize care for patients and their families and improve health outcomes."

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Once-Weekly Carfilzomib as Safe, Effective as Twice-Weekly Treatment in Newly Diagnosed MM

RECENTLY PUBLISHED RESEARCH INDICATES that patients newly diagnosed with multiple myeloma (MM) can be treated with carfilzomib (Kyprolis) once a week instead of twice. According to researchers, a once-weekly 70 mg/m^2 dose of the proteasome inhibitor is as safe and effective as twice-weekly 36 mg/m^2 doses while also providing a more convenient treatment schedule.

Currently, carfilzomib is indicated for twice-weekly treatment of patients with relapsed and/or refractory MM, but given its demonstrated efficacy, the treatment has been assessed as upfront therapy in combination with lenalidomide–dexamethasone or with alkylating agents, such as melphalan–prednisone, for newly diagnosed patients.

"Despite the great results yielded by the introduction of carfilzomib, treatment compliance and quality of life of young active patients, as well as those of elderly patients with reduced mobility, are burdened by the need for frequent visits to the outpatient clinic for carfilzomib dosing," wrote the researchers. "In this view, a shift from the current twice-weekly to a once-weekly dosing schedule would decrease by 50% the patient visits to healthcare facilities, with a subsequent improvement in quality of life and a reduction in drug and healthcare costs."

Pooling data from the phase 1/2 IST-CAR-561 and phase 1 IST-CAR-506 studies comparing once-weekly (70 mg/m^2) and twice-weekly (36 mg/m^2) treatment with carfilzomib plus cyclophosphamide and dexamethasone, the researchers identified 199 transplant-ineligible patients with newly diagnosed MM across 14 sites in Italy. The patients received either once-weekly or twice-weekly treatment for 9 four-week induction cycles. Following the induction period, 90 patients received maintenance therapy with carfilzomib alone.

Data showed that no significant difference in progression-free survival (PFS) existed between the 2 treatment schedules, with a median PFS of 35.7 months among patients receiving once-weekly carfilzomib and a median PFS of 35.5 months among patients receiving twice-weekly treatment.

After 3 years of follow-up, 47% and 49% of patients in the once-weekly and twice-weekly groups, respectively, were alive and progression-free. Median overall survival was not reached for either group, with 70% of patients in the once-weekly group and 72% of patients in the twice-weekly group being alive at 3 years.

Even when adjusting for age, frailty, and other factors, the researchers observed no significant differences in the risk of progression or death.

The most commonly reported adverse events (AEs) included acute kidney injury and hypertension. These events led to a dose reduction of carfilzomib in 18 (29%) of patients receiving once-weekly treatment and in 17 (30%) patients receiving twice-weekly treatment. Meanwhile, 17 (27%) patients in the once-weekly group and 17 (30%) patients in the twice-weekly group had to discontinue therapy as a result of AEs that included cardiac injury, infections, and thromboembolism.

"Of note, delivering 70 mg/m^2 of carfilzomib in a single dose did not increase the risk of grade 3 to 5 hematological (24% vs 30%) and nonhematological (38% vs 41%) AEs, as compared with a twice-weekly administration of 36 mg/m^2 of carfilzomib," explained the researchers, who added that no new cardiovascular safety risks were identified with the single dose.

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Despite Involvement in Cancer Treatment Decisions, PCPs Lack Knowledge, Confidence

AS THE HEALTHCARE SYSTEM continues to strive to be patient-centered, team-based care has emerged as an important tool for improving quality of care and patient satisfaction, particularly in oncology. Within the care team, the primary care provider (PCP) plays an integral role, as they are often the provider managing the patient's other comorbidities and general care, and thus they have a better understanding of the patient's preferences and values. However, while patients often come to these providers first to discuss cancer treatment options, PCPs report significant knowledge gaps regarding these treatments.

According to a study in *Cancer*,[1] one-third of PCPs reported participating in breast cancer treatment decisions with their patients, but a significant number of these PCPs nonetheless indicated that they were not comfortable with or did not feel that they had the necessary knowledge to participate in the treatment decision-making process.

"Primary care physicians may be involved in cancer care earlier than we thought," Lauren P. Wallner, PhD, MPH, a health services researcher at the University of Michigan Rogel Cancer Center, said in a statement.[2] "If we are going to promote their involvement, we may need to start doing that earlier, around the time of initial treatment, and ensure [that] PCPs have the information they need to effectively participate in the decision-making process."

Drawing on data from the Individualized Cancer Care study, which included 1077 women with early-stage breast cancer and their 517 PCPs, the researchers identified women aged 20 to 79 years from Los Angeles County, California, and Georgia who had been diagnosed between 2013 and 2015. PCPs were asked whether they had discussed surgery, radiation, or chemotherapy options with their patients and how comfortable they were with doing so.

Survey answers revealed that 34% of PCPs had discussed surgery options with their patients, 23% had discussed radiation, and 22% had discussed chemotherapy. Across all 3 treatment options, PCPs who reported ability to participate in the decision-making process were more likely to have these discussions and have them more often.

However, the survey also revealed that among PCPs who discussed surgery options with their patients, 22% reported not being comfortable having those conversations, 17% reported that they did not have the necessary knowledge to do so, and 18% reported that they lacked the confidence to do so.

Similar findings were seen across the other 2 treatment options. Sixteen percent of PCPs who discussed radiation with their patients reported that they were not comfortable having those discussions, 9% reported not having the knowledge to help with these discussions, and 14% reported that they lacked the confidence to do so. Among PCPs who discussed chemotherapy with patients, 25% reported not being comfortable, 9% reported not having the knowledge, and 16% reported not having the confidence to help with these decisions.

Reflecting on these findings, the researchers emphasized the need for efforts to better communicate with PCPs and to educate them about the specifics of cancer treatments.

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Treatment Advances Avert More Than Half a Million Breast Cancer Deaths Over 3 Decades

AS MANY AS 614,500 breast cancer deaths have been averted since 1989, according to a new study.[1] This figure can be attributed to greater usage of preventive screening measures as well as advancements in treatment.

Beginning in 1969, the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program has annually gathered data on the frequency of breast cancer and associated mortality rates in the United States. It was observed that these rates among afflicted women increased 0.4% annually from 1975 to 1990. It was then found that mortality rates began to decrease 1.8% per year from 1990 to 1995, 3.4% from 1995 to 1998, and 1.8% from 1998 to 2015. Cumulatively, breast cancer mortality rates among females between the ages of 40 and 84 years dropped by 41.6% from 1989 to 2015.

The authors applied age-adjusted population and mortality rate data from the SEER program to predict the total amount of breast cancer deaths avoided by preventive screening and advancements in treatment from 1989 to the present. Four different assumptions about background mortality rates were applied to approximate deaths avoided for women aged between 40 and 84 years. These assumptions included an increase of 0.94% per year in the absence of screening or treatment, an increase based on the trend from 1979 to 1989, an increase of 0.4% per year based on what was observed from 1975 to 1990, and a flat mortality rate since 1989. The approximations were calculated by measuring the difference between SEER-reported and background mortality rates for each 5-year age group then multiplied by the population for each group.

SEER data were used to project total yearly breast cancer deaths deterred in 2012 and 2015, and estimated SEER data were used to evaluate deaths avoided in 2018. Research conducted by the authors has shown the total number breast cancer deaths prevented since 1989 ranged from 237,234 to 370,402 in 2012, from 305,934 to 483,435 in 2015, and from 384,046 to 614,484 in 2018. Applying the same assumptions to the approximated amount of total lives saved in a single year, data show these numbers fall between 20,860 and 33,842 in 2012, between 23,703 and 39,415 in 2015, and between 27,083 and 45,726 in 2018.

Breast cancer mortality rates steadily increased prior to 1990, according to the data. In the 1980s, advances in treatment, including chemotherapy and hormonal therapy, entered clinical practice. It is estimated that together they were successful in reducing mortality rates by 1989.

During the same time period, physicians began to advocate that early detection was also crucial for saving lives. As a result, screening mammography grew in popularity and became more broadly clinically practiced. While the long-term benefits of mammography were shown to be invaluable in the saving of thousands of lives, those benefits did not accrue immediately. Research involving randomized controlled trials showed that preventive screening "require[d] 5 to 7 years to demonstrate an evident mortality reduction due to the longer interval between screen detection and prevented death." The prevalence of mammography screening has drastically fluctuated since its inception. Data released by the CDC's National Health Interview Survey show that in 1987, 29% of women aged more than 40 years participated in screening within a 2-year window. The same survey reported that mammography was at the height of its popularity in the year 2000, at 70%, then alarmingly fell to 64% in 2015. Presently, only about half of women aged more than 40 years receive recommended screening mammography.

"The best possible long-term effect of our findings would be to help women recognize that early detection and modern, personalized breast cancer treatment save lives, and to encourage more women to get screened annually starting at age 40," R. Edward Hendrick, PhD, of the University of Colorado School of Medicine and one of the study's authors, said in a statement. ◆

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AJMC®TV interviews let you catch up on what's new and important about changes in healthcare, with insights from key decision makers—from the clinician, to the health plan leader, to the regulator. When every minute in your day matters, *AJMC*®TV interviews keep you informed. Access the video clips at ajmc.com/interviews.

Produced by Jaime Rosenberg, Anthony Berberabe, and Danielle Ternyila

Ben Jones, Vice President, Government Relations and Public Policy, McKesson Specialty Health

What are some recent policies that are having the biggest impact on cancer care delivery?

A number of policies have really taken shape over the past 18 months and significantly transformed community oncology and cancer care in general. One of them is around site-of-service parity; that is establishing a level reimbursement field for certain services on a go-forward basis and even in the last round of rulemaking for clinic office visits. Changes to 340B have had an impact on community cancer care and cancer care in general.

But by and large, the biggest proposals are those that are pending. The president has released his drug pricing blueprint that contained a number of changes—seismic shifts—in policy for [Medicare] Part B reform. They include step therapy, a relaxing of protected classes, but also a new international index model, the International Pricing Index Model, that would completely change the way Part B drugs are acquired, stored, and administered to patients. I really think this could lead to a lot of disruption in access to timely care for practices across the country.

Are there unique challenges that community practices face regarding reimbursement?

In 2015 the Bipartisan Budget Act instituted site neutrality on a go-forward basis for off-campus outpatient facilities. Since then, there's been an expansion to clinic office line visits, and that could go further. But by and large today, there's still a big disparity in reimbursement, where a hospital practice or a hospital-based cancer care center will receive twice as much as the outpatient facility for the exact same service. And this is incentivizing hospitals to consolidate, and we will have situations in which a community cancer center changes nothing but the sign on the door, and then all of a sudden, the patient's out-of-pocket costs go up and the cost of Medicare goes up.

The administration—HHS Secretary Alex Azar and President Donald Trump—have indicated that they want to look into this. They made a proposal in the last physician fee schedule. They want to explore site neutrality for drug administration services; that was included in the drug pricing blueprint. And this is also something that Congress is becoming well aware of in trying to figure out how they can expand what they passed in 2015, to try to come to some sort of parity in reimbursement without disrupting access to care in hospital or community-based settings.

Allen Lichter, MD, FASCO, Senior Partner, TRG Healthcare

How is telehealth allowing community oncologists to reach more patients and improve care?

I think today telehealth is present in oncology in specific areas. Obviously, our imaging colleagues use telehealth to transport images all around the world, and if you go to an emergency department at night, your image is often read in another part of the world, where it's daylight. Our pathology colleagues are using telecommunications to transmit images. Our patients are sometimes sending images—I certainly sometimes let my dermatologist take a look at certain things on my skin to save me a trip to the office.

Another area is patient engagement, trying to keep using technology—often an app or a synthetic conversational agent, called a chatbot—to ask the patient how they're doing, to check up on symptoms, and to allow patients to tell us much earlier about something that's going on and head it off at the pass and not react to it as a crisis. But the future is going to have so much more. We're going to have remote sensors. We're going to be able to monitor physiologic processes. We're going to be able to diagnose and eventually provide therapeutic interventions remotely.

Another area that oncology touches with telehealth is the second-opinion process. Many major institutions and cancer centers will do second opinions through telemedicine versus having the patient travel for hundreds or thousands of miles.

There's a presence now, but the future is extremely interesting.

The concept that as patients, the only way [you and I] can have an interaction with the healthcare system is to drive to an office or a hospital, wait in the waiting room, go back, get into a gown, and wait for the healthcare provider to come into the room—that's certainly the paradigm that I grew up in and is the paradigm that predominates in medicine today, but there are so many ways to deliver effective healthcare. It doesn't necessarily involve that face-to-face interaction. And believe me, I think face-to-face is the essence of medicine. But sometimes we need to expand our capacity and to be more convenient and fit into the patient's life better. That's where I see us making strides.

Toby Campbell, MD, MSCI, Professor of Medicine, University of Wisconsin Carbone Cancer Center

When should end-of-life care discussions take place with patients with a cancer diagnosis? Are they happening at the right time?

End-of-life care discussions should happen with patients well before you're at that point. Just imagine that you're an oncologist, and you're working with a patient—maybe you're working with them for months or a few years—and you have a discussion about, "Hey, you've got this cancer, and here's a treatment." And then, "Oh, there's bad news, but I have another treatment." At some point, you run out of treatment options. And then you face a discussion about talking about end-of-life care. Well, that's an awfully big discussion, and it's a really impactful and momentous one.

I think that the strategy that makes the most sense is to walk yourself back to the beginning, when you identify that a patient has a disease that cannot be cured. At those early moments, before you even face any crucible moments, you start to introduce it. And then you introduce it again at any time of progression. And that way, when you reach that point, where you do not have any additional treatment options that make sense, [it's a less difficult conversation]. The patient is likely already aware, but it might sound something like, "You know how we've been talking over time that at some point we were going to reach a place where I didn't have any additional treatment options? You know, we're there."

And odds are that conversation, if you imagine the one that you might have had to have without having any preparation versus that, it really alters the

arc of the whole thing. But it starts—the inflection point can be modest, can be mild, months or years earlier, as opposed to a giant inflection point if you wait until the end.

So I don't think that oncologists have this conversation as often as they could. We certainly have some data that suggest patients have a poor understanding of whether their disease is curable. So it certainly suggests that we could be doing this earlier.

Howard Burris III, MD, FACP, FASCO, President, Clinical Operations and Chief Medical Officer, Sarah Cannon Research Institute

As next-generation testing becomes more important, with a growing number of approved targeted therapies, what is needed from a policy perspective to ensure access to these tests?

Access to these tests and getting the various stakeholders together [are what is needed]. If I were a payer at an insurance company, my question wouldn't be whether I approve the testing; it would really be how you could be prescribing this new therapy, this relatively expensive therapy, without having a molecular profile on the patient. I think much as we've had legislation regarding access to clinical trials, this sort of national education that [patients with] cancer should have [access] to getting a test performed would be key.

A good first step has been the FDA approving some of these tests and then Medicare providing reimbursement. So I feel optimistic that we're moving in a direction where we're going to begin to get policy makers across the country, the physicians across the country, to understand this is a critical piece of information [patients with] cancer should know.

Basit Chaudhry, MD, PhD, Founder, Tuple Health

With results from the Oncology Care Model (OCM) performance period 3 (PP3) now out, did you see improvement over performance periods 2 and 1?

It's interesting. In PP3, 33% of practices were able to achieve a shared savings. I think that was somewhat concerning because that has stayed stable since PP2. In PP2, 33% of practices [also] achieved a savings. In PP1, it had been 25%. So between PP1 and PP2, we saw a growth or improvement. I personally was hoping that we'd continue to see aggregate improvement in performance in terms of achieving a shared savings. That unfortunately didn't happen, so that aspect of performance leveled out.

The other important thing about the results from PP3 is that we've gotten additional data on what has happened in the true-up period. Medicare claims can be sent in about a year after a service is provided and in performance-based models, you continue to look at what happens as claims roll out or into Medicare. So for PP1, the number of practices that retained a shared savings went from 25% to 20%. For PP2, it went from 33% to 25%. There are 2 trends, I think, that are concerning with the results of shared savings. One is that we've leveled out in terms of the proportion of practices that have achieved a shared savings, and then [with] the true-up process, we're seeing a regression of the results.

Now, from what we understand from Medicare, different practices are getting shared savings at different times. So overall, from what they've said, from the start of the program, around 50% of all the participants have achieved at least 1 shared savings. I feel like that's progress in certain respects, but in aggregate, I think there's still concern over where practices are. The other thing I think is how you look at performance versus the benchmark. The benchmark doesn't take into account the amount that's provided from the MEOS [Monthly Enhanced Oncology Services] payments or the 4% discount, which is supposed to neutralize that. So practices are doing better with respect to the benchmark; about three-quarters of practices, from what we understand, are under benchmark. But there's still a concern there on how people are doing with respect to performance-based payments, and the upshot of it is that if practices are going to stay in the OCM, a good proportion most likely would need to go to a down-sided risk model.

Katie Goodman, BSN, RN, CCRP, Director, Clinical Research, Florida Cancer Specialists & Research Institute

How is community oncology poised to shape the future of cancer care regarding clinical trials?

Community oncology practices are where most patients receive their treatment. So if we need patients to participate in clinical trials to get the answers, to move the needle on the science, to know whether this next treatment will be effective, we have to bring the trials to where those patients are being treated. We also know that patients aren't going to participate in a clinical trial if it's too much of a burden on them. They have to travel great distances to participate. [Patients with] cancer are usually in the clinic once a week at the very least, if not more, and that is too great a burden on a patient. We want the answers, we want the science, and the only way we can really do that is to bring the trials to the patients where they live. So it is very important to us in the practice that I work at that we continue to offer clinical trials in the community setting.

Lee Schwartzberg, MD, FACP, Executive Director, West Cancer Center

Liquid biopsies have shown promise in lung cancer and most recently in breast cancer. Do you think use of these biopsies will become more prevalent in the future?

I think liquid biopsies are going to be very important in the precision oncology world of tomorrow. I just returned from AACR [American Association for Cancer Research Annual Meeting], and there were many presentations in 2019 about liquid biopsies. The technology is developing very quickly. The idea that tumors shed both cells and circulating tumor DNA, as well as some other subcellular molecules like microRNA and proteins into the bloodstream, means that the blood is a rich source [for] understanding the dynamics of how tumors grow and shrink. So as the technology improves, and as the studies are done to show concordance against tissue biopsies, we're going to see liquid biopsies used in multiple directions.

Right now, they're good for when you don't have a tissue biopsy available or there's a limited sample or not enough to do next-generation sequencing; for example, we can get those results from a liquid biopsy. I think in metastatic cancer, it's going to be very useful to monitor patients to see what happens because tumors unfortunately change over time. They can find resistance mechanisms to get around some of the medicines we use. And of course, there's a lot of interest in early diagnosis using liquid biopsies, and many companies are working on tests that can be used broadly to screen patients for cancer when they have no symptoms. So we're very excited about the entire spectrum of liquid biopsies. There's a lot of work that needs to be done. There are a lot of clinical trials to show the clinical utility, but the validation—technical validation and the clinical validation—has already largely been done. ◆

A Step in the Digital Direction: From Paper Logs to Electronic Data Capture

Nate Brown, BA; Evelyn Siu, BA; and Janet Donegan, ANP-BC, AOCN

CONTINUED FROM COVER

One piece of documentation kept in this shadow chart is the AE log. AEs must be documented at every patient interaction and entered using standard terminology. The paper-based AE documentation (**Figure 1**) process is cumbersome in many aspects.

The Paper Log: A Conventional Solution

For decades, the paper log has been the accepted tool for clinical research staff, data coordinators, and primary investigators/sub-investigators (PIs/SubIs) for recording AEs in a prospective clinical trials. Each of those individuals is required to enter, edit, review, or sign off on every detail of log information. The clinical research coordinators (CRCs) first document the AEs in the paper log. Next, the PI/SubI reviews, completes, and signs off on these events before the data coordinator can use the written information to painstakingly type the exact data into the electronic data capture (EDC) system. However, each staff member physically sits in a different place, forcing a "hot potato" hand-off of the log throughout the day.

Potentially the Wrong Place at the Wrong Time

Additionally, AEs must be reviewed at every patient interaction (each visit, phone call, etc). This results in a risk that the CRC is interacting with the patient at the same time the PI/SubI is reviewing the log. Therefore, the CRC may not have the log on hand to immediately document the AE reported by the patient. Based on many conversations between Flatiron Health staff and those in clinical practices, it is clear that this cumbersome, multistep process means that the log may be in the wrong place at the wrong time.

Common Terminology Criteria Entry: A Manual Process

In addition to coordinating access to the paper log, recording the specific AE term is also a time-consuming process. All AEs must ultimately be reported using the standard Common Terminology Criteria for Adverse Events (CTCAE), a guideline that assesses the seriousness of the AE that occurred. Today, because the process is mostly paper-based, research staff must flip through about 800 terms and grades in PDFs and mini-booklets

Figure 1. Example of Today's Paper-Based Adverse Event Log

Adverse Event Log

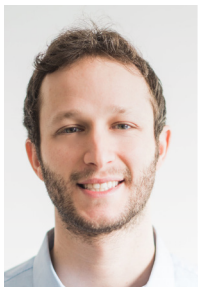
Patient ID

#	Adverse event term (CTCAE 4.03)	*Is this a Serious Event?	Start/Stop date (ddmmyyyy)	Grade	Relationship to study treatment	Action taken with study treatment	Relationship to non-study treatment	Action taken with non-study treatment	Outcome	Concomitant or additional treatment given	Investigator Review
1		[ ] Yes [ ] No	Start Date: _____ Stop Date: _____	[ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5	[ ] Not related [ ] Unlikely related [ ] Possibly Related [ ] Related	[ ] Not applicable [ ] Unknown [ ] Dose not changed [ ] Dose Reduced [ ] Drug withdrawn	Non-study treatment: _____ [ ] Not related [ ] Unlikely Related [ ] Possibly Related [ ] Related	[ ] Not applicable [ ] Unknown [ ] Dose not changed [ ] Dose reduced [ ] Drug withdrawn	[ ] Resolved [ ] Continuing [ ] Resolved with residual effect [ ] Unknown [ ] Change in grade [ ] Discontinued study due to AE		
2		[ ] Yes [ ] No	Start Date: _____ Stop Date: _____	[ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5	[ ] Not related [ ] Unlikely related [ ] Possibly Related [ ] Related	[ ] Not applicable [ ] Unknown [ ] Dose not changed [ ] Dose Reduced [ ] Drug withdrawn	Non-study treatment: _____ [ ] Not related [ ] Unlikely Related [ ] Possibly Related [ ] Related	[ ] Not applicable [ ] Unknown [ ] Dose not changed [ ] Dose reduced [ ] Drug withdrawn	[ ] Resolved [ ] Continuing [ ] Resolved with residual effect [ ] Unknown [ ] Change in grade [ ] Discontinued study due to AE		
3		[ ] Yes [ ] No	Start Date: _____ Stop Date: _____	[ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5	[ ] Not related [ ] Unlikely related [ ] Possibly Related [ ] Related	[ ] Not applicable [ ] Unknown [ ] Dose not changed [ ] Dose Reduced [ ] Drug withdrawn	Non-study treatment: _____ [ ] Not related [ ] Unlikely Related [ ] Possibly Related [ ] Related	[ ] Not applicable [ ] Unknown [ ] Dose not changed [ ] Dose reduced [ ] Drug withdrawn	[ ] Resolved [ ] Continuing [ ] Resolved with residual effect [ ] Unknown [ ] Change in grade [ ] Discontinued study due to AE		
4		[ ] Yes [ ] No	Start Date: _____ Stop Date: _____	[ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5	[ ] Not related [ ] Unlikely related [ ] Possibly Related [ ] Related	[ ] Not applicable [ ] Unknown [ ] Dose not changed [ ] Dose Reduced [ ] Drug withdrawn	Non-study treatment: _____ [ ] Not related [ ] Unlikely Related [ ] Possibly Related [ ] Related	[ ] Not applicable [ ] Unknown [ ] Dose not changed [ ] Dose reduced [ ] Drug withdrawn	[ ] Resolved [ ] Continuing [ ] Resolved with residual effect [ ] Unknown [ ] Change in grade [ ] Discontinued study due to AE		

*Serious adverse events must be reported as per the protocol requirements (e.g. sending the SAE report form to safety within 24 hours of awareness)

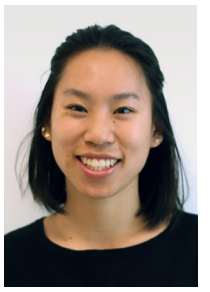
Investor Signature: _____ **Investigator Signature Date (dd/mm/yyyy):** _____

AE indicates adverse event; CTCAE, Common Terminology Criteria for Adverse Events.



BROWN

Nate Brown, BA, is director, product marketing and strategy, Flatiron Health.



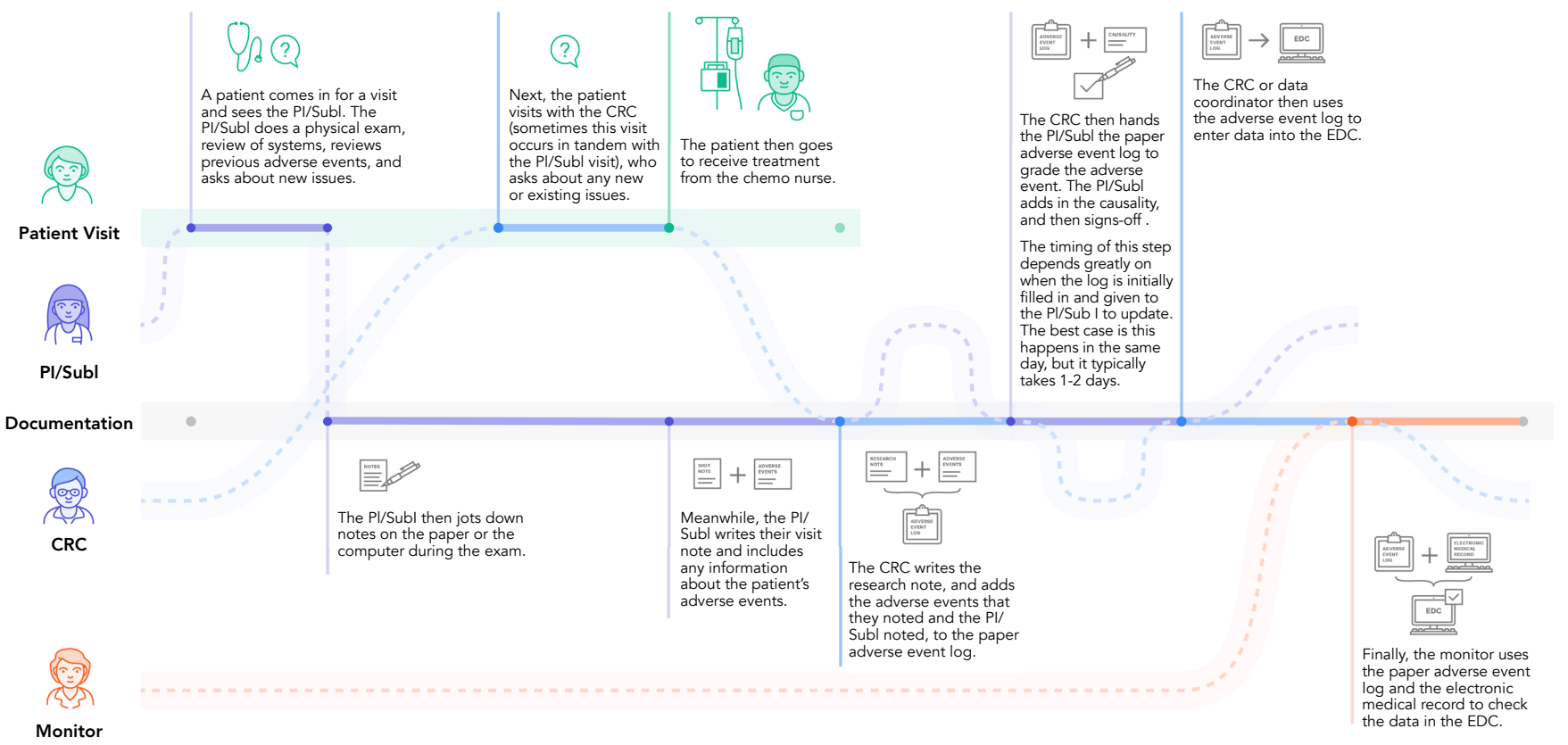
SIU

Evelyn Siu, is associate, product marketing and strategy, Flatiron Health.

DONEGAN

Janet Donegan, RN, ANP-BC, AOCN, is director, clinical oncology, Flatiron Health.

Figure 2. The Journey of the Adverse Event Log



CRC indicates clinical research coordinator; EDC, electronic data capture; PI/SubI, primary investigator/subinvestigator.

to find the correct term. Additionally, multiple versions of CTCAE are in use today, and each trial may reference a different version. Research staff must be careful to ensure that the version of the CTCAE term they use matches the CTCAE version of the trial.

Data Messiness and Interpretation

Finally, these logs quickly become crowded and messy due to the fact that multiple contributors write in and edit each log. Again, because of the manual and handwritten process, research team members and/or monitors often express frustration with the trouble of interpreting the data. This leads to questions that the research team spends time fielding, but these questions could have been avoided if the data had been more legible or easier to follow.

Trying a Different Approach: Integrating AE Documentation Into the EHR

Over the years, we've heard from the Flatiron Health network of community-based practices that for the reasons stated, paper-based research documentation—and specifically AE documentation—is a critical pain point. In 2017, we kicked off a brainstorming session with some of the 350-plus community leaders at our annual provider conference to explore different solutions. From these early conversations, it became clear that digitizing the AE workflow in the EHR could be a way to alleviate some inefficiencies of the paper-based workflow.

As the idea of electronic AE capture began to take shape, we conducted on-site user research with 10 selected practices. These sites represented a range of research practices, differing in size as well as phase (ie, early- through late-phase trial sites). We then partnered closely with 5 of these sites, which became our beta partners. A beta partner is a practice that tests our initial product versions and works closely with us throughout the product development process to ensure that our solutions are intuitive and effective for practices across the provider network.

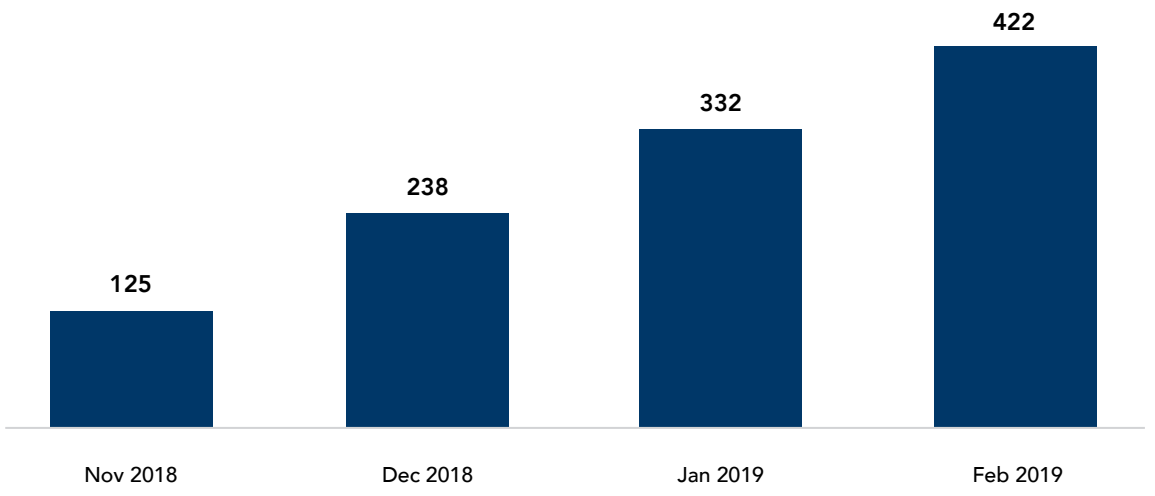
At Flatiron Health, we believe that the only way to build an effective product is to start with a clear understanding of the problem. In this case, we needed to observe research teams' workflows and to conduct extensive interviews to better understand the current landscape of the AE documentation process. For the AE feature in OncoEMR® alone, we've spent more than 40 hours to date on the phone and in person (including several on-site visits), improving the workflow with our development partners.

Across user research visits, we observed key trends in the core process for AE documentation (with slight variability) across sites **(Figure 2)**.The research team at a site can find out about a patient's AE in several different ways: The patient may come to the practice for treatment and/or a physician visit and tell the physician, CRC, or chemo nurse; a patient's lab values may come back abnormal; the patient may call the practice to say they are experiencing an issue; or the patient is hospitalized, which the practice learns from the patient, caregiver or hospital.

However, based on our beta partner research, it is most common for practices to find out about a patient's reported AE through the patient visit, so our user research focused primarily on this process:

- A patient comes in for a visit and sees the PI/SubI. A PI/SubI does a physical exam and review of systems, reviews previous AEs, and asks about new issues. The PI/SubI then jots down notes on paper or a computer during the exam. Next, the patient visits with the CRC (sometimes this visit occurs in tandem with the PI/SubI visit), who asks about any new or existing issues. The patient then receives treatment from the chemotherapy nurse.
- Meanwhile, the PI/SubI writes the visit note and includes any information about the patient's AEs. The CRC writes the research note, adding the AEs that they and the PI/SubI noted to the paper AE log. The CRC then hands the PI/SubI the paper AE log to grade the AE (eg, serious). The PI/SubI adds in the causality, then signs off. The timing of this step depends greatly on when the log is initially filled in and given to the PI/SubI to update. In the best-case scenario, this happens in the same day, but it typically takes 1 to 2 days. The CRC or data coordinator then uses the AE log to enter data into the EDC.

Figure 3. Number of Adverse Events Added in OncoEMR Over Time (Cumulative)*



*includes test patients

Finally, the monitor uses the paper AE log and the EHR to check the data in the EDC.

In each of these visits, we also learned about some overarching needs to address in an AE feature. For example:

- A need to show different users only the key information that is relevant to their needs:
  - PI/SubIs may want to see only information that requires action from them. For instance, "I don't want to see the old or closed-out AEs," said Ted Arrowsmith, MD, a PI at Tennessee Oncology, Chattanooga.
  - Previously in the paper logs, there could be several pages of resolved AEs that the PI/SubI would need to flip through before reaching AEs that required action from them.
  - However, monitors would need to see the comprehensive change history of who changed what, and when.
- A need for structure but room for some flexibility, such as the ability to:
  - Integrate with other physician workflows, yet not affect the workflows of physicians who are not involved in research.
  - Provide easy access to or the integration of CTCAE names and grades, such as with a smart-search or auto-suggest function.
  - Switch easily between CTCAE versions that differ based on the trial.
  - Allow for modifying previously entered data while tracking a comprehensive change history.

Moving From Initial Product to Real-World Readiness

In April 2018, we presented the first version of our feature to our beta partner practices. During this phase of feature development, we continued to learn more about the specific use cases for electronic AE documentation, and we gained more specific feedback about changes to our product. For example, some practices suggested specific terminology changes. Another practice pointed out the importance of specifically calling out AEs that are dose-limiting toxicities (DLTs) for early-phase trials. Additionally, the paper log had other flexibilities that we hadn't accounted for in the initial version of the electronic log, such as the ability to add an AE that was not listed as a standard CTCAE term. Gerald Falchook, MD, director, Sarah Cannon Research Institute at HealthONE, Denver, expressed that he "wouldn't want to be boxed in" by the initial version of the digitized workflow.

The electronic AE capture that exists today in OncoEMR® includes functionality that is a direct result of feedback from our beta partners. These improvements include (but are not limited to):

- Specifying a unique AE term, in the cases when AE terms do not fit within the CTCAE terminology,
- Allowing capture of AEs by partial dates (month/year) when teams need to capture AE timestamps different from the month/day/year format,
- Displaying AEs in order of date added, not date edited, because users often prefer to find AEs by when they were added, and
- Adding the DLT, AE of significant interest, and serious AE labels for users to quickly see AEs of interest.

We know that the transition from paper to electronic documentation is not always easy. As burdensome as the paper-based AE documentation process is, it is familiar. Adopting new workflows requires staff training and time for learning, time that community oncology practices cannot always afford to spare. "We've used [the AEs feature] on 3 to 4 trials, and all the patients on the new trials. It takes a little getting used to," said Wendy Koopman, a research manager at Cancer & Hematology Centers of Western Michigan. "It was helpful when we worked through different scenarios, and people could ask questions [to the Flatiron team]. Hands-on is [the] best way to learn." To adopt this workflow, not only will the research staff and physicians need to change their process, but monitors will also have to adapt to a new electronic log.

That being said, even the FDA is beginning to communicate the benefits of capturing clinical trial data directly in the EHR. In a recently released guidance on the use of EHRs in clinical investigations, the FDA stated, "Fully integrated systems allow clinical investigators to enter research data directly into the EHR. This may involve, for example, use of research modules, use of research tabs built into the EHR system, or use of custom research fields within the EHR system for data that are entered for research purposes."[1] This excerpt sheds light on the industry shift toward electronic research documentation workflows.

We are seeing continued uptake of the AE documentation feature among our beta partners, integrating it into their workflows. During the initial launch of the feature in November 2018, we observed 125 AEs added to clinical trial regimens, which grew to a total of 238 added by December 2018. By February 2019, a total of 422 AEs had been added using the feature in OncoEMR **(Figure 3)**.

Our beta partners have also shared their enthusiasm about the benefits they have experienced from this change. A clinical research coordinator, Tiffany Cason, from Tennessee Oncology in Chattanooga, reported on the efficiency compared with her old CTCAE workflow: "I don't use my paper CTCAE booklet anymore, because it's faster to find the CTCAE term in OncoEMR." Arrowsmith said he sees value in the consistency of the data captured: "The adverse event log in OncoEMR makes people choose actual adverse event terms. The more the source data from providers/coordinators can match the EDC, the better quality those data will be and the more bulletproof it is to audits and monitoring."

Electronic AE documentation has recently become available to all practices that subscribe to OncoEMR, and we will continue to improve the feature's functionality as we hear feedback. We recognize that this shift will require the participation of the entire research team in order for workflow changes to occur. We also recognize that digitizing this otherwise manual process is just one small step in helping research departments reduce the burden of research documentation. We're excited to partner with our practices to develop something that generates such excitement for our research teams. In the words of Kim Tucker, MT HEW, a senior oncology site manager from Tennessee Oncology in Chattanooga, "[The] adverse event log is the best thing I've seen in 10 years. We can't wait to start using this." A long road waits ahead, but we're constantly driven by the passion of our practices to move forward. ◆

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The Conundrum of Antibacterial Use in Neutropenic Patients Undergoing Chemotherapy for Hematologic Malignancy or HSCT

Sanjeet Singh Dadwal, MD

DADWAL

Sanjeet Singh Dadwal, MD, is a clinical professor in the Department of Medical Specialties, Division of Infectious Disease at City of Hope, Duarte, California.

CONTINUED FROM COVER

However, results from 2 systematic reviews by Gafter-Gvili et al, first in 2005 and later in 2012, demonstrated that antibiotic prophylaxis was associated with a mortality benefit, based on pooling data, along with reduction in the incidence of fever and bacteremia.[3,4] Based on these results, many clinicians have adopted universal prophylaxis to prevent infection in patients who develop neutropenia from chemotherapy for HM or HSCT. Furthermore, in those who develop fever while neutropenic, empiric broad-spectrum antibacterial treatment with activity against gram-negative bacteria, especially *Pseudomonas aeruginosa*, and coverage for gram-positive infection per clinical indication is suggested. Clinical guidelines suggest continuation of empiric antibacterial agents until the resolution of neutropenia, even when no organism or source is identified.[5]

Inconsistency in Guidelines

US clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Clinical Oncology recommend use of fluoroquinolones in high-risk patients, defined as those with an absolute neutrophil count <100/mm^3 and neutropenia with an expected duration of >7 days.[6] Infection prevention guidelines from the National Comprehensive Cancer Network also recommend fluoroquinolones as first-line prophylaxis in high-risk neutropenic patients.[7] Meanwhile, Australian and European guidelines recommend against routine prophylaxis because of a lack of mortality benefit and concern about emerging resistance in gram-negative organisms.[8,9]

In a meta-analysis of literature published between 2006 and 2014, Mikulska et al concluded that there was no "mortality benefit" from antibacterial prophylaxis.[10] Although extensive literature on the management of neutropenic fever exists, discussions with colleagues across cancer centers reveals a lack of consensus on the practice of prophylaxis, and de-escalation after initiation of empiric therapy varies despite the guidelines.

Concern About Antimicrobial Resistance

The emergence of antimicrobial resistance and toxicity with prophylaxis and prolonged courses of broad-spectrum antibiotic use in neutropenic patients represents a serious issue. Potential burden of antibiotic resistance was assessed in a 2015 modeling study.[11] Infection with multidrug resistant organisms (MDROs) such as the ESKAPE group (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species) is now a major management challenge.[12,13] The concerns with fluoroquinolone prophylaxis center on an increase in infections from coagulase-negative staphylococci, fluoroquinolone-resistant viridans streptococcal infections, emergence of extended-spectrum β-lactamase enzyme producing *Enterobacteriaceae*, and induction of resistance to carbapenems in *Pseudomonas* species and *Clostridium difficile* infection. In a study from a major cancer center using routine fluoroquinolone prophylaxis, the rate of fluoroquinolone-resistant *Escherichia coli* infections increased from 28% to 60% over 9 years.[14] Beyond concerns about MDROs, fluoroquinolones carry a risk of various adverse effects, with the FDA having expanded the black box warnings on their use. These include risks for aortic aneurysm, retinal detachment, and tendinitis.[15]

Research on the damaging impact of antimicrobials on the gut microbiome is also emerging. Investigators have demonstrated the harmful effect of antibiotics, specifically loss of microbial diversity, which has led to a higher risk of acute graft-versus-host disease (aGVHD) and an independent risk factor for mortality in allogeneic HSCT recipients.[16-18] An increased rate of bacteremia has also been associated with alteration of the gut microbiome. This information is very important in assessing the approach to universal antibacterial prophylaxis and continuation of empiric therapy until resolution of neutropenia.

"It is critical that we as healthcare providers seriously consider the benefits and harms of antimicrobial prophylaxis and empiric therapy for neutropenic fever."

—Sanjeet Singh Dadwal, MD

The morbidity and mortality associated with MDRO infections are substantial, as is the cost of care compared with that of a non-MDRO infection.[19] Efforts to reduce the burden of MDRO infection would entail minimization of inappropriate prescribing, effective infection control, and, in the context of HM/HSCT, the use of caution with prophylactic approaches and prolonged empiric treatment. Results from recent studies suggest that not using antibacterial prophylaxis for chemotherapy-induced neutropenia is safe.[20] In addition, in reporting results from a cohort of allogeneic HSCT recipients, a European group suggested the safety of de-escalation/stopping of empiric antibiotics in patients who had no identifiable source and had become afebrile.[21] In our own personal experience, during the era of routine fluoroquinolone prophylaxis (since 1998), the rate of fluoroquinolone resistance in bloodstream bacterial isolates increased from 47% over a period of 6 years to 61% in 2004.[22] In 2005, we restricted its use, and since then, the rate of fluoroquinolone-resistant bacterial isolates has declined for patients in our institution to 40% in 2018 (S.S.D. et al; unpublished data).

Conclusion

It is critical that we as healthcare providers seriously consider the benefits and harms of antimicrobial prophylaxis and empiric therapy for neutropenic fever. Because the mortality benefit from prophylaxis is in question, efficacy of fluoroquinolone prophylaxis in the context of MDRO colonization may be ineffective. There is emerging data on loss of gut microbiome diversity and increase mortality/aGVHD in allogeneic HSCT patients, even though IDSA guidelines suggest continuing empiric therapy until neutropenia resolution and mention that de-escalation should be considered. It is imperative that we revisit the dogma surrounding the antibacterial prophylaxis and unfettered empiric antibacterial therapy. ◆

ADVERSE EVENT MANAGEMENT

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POLICY UPDATE

Providers, Industry Raise Concerns About CMS Plan for CAR T-Cell Reimbursement, Reporting on PROs

Mary Caffrey

CONTINUED FROM COVER

Since February 15, 2019, when CMS issued its proposal,[3] cancer centers that have been losing money on CAR T-cell treatments have raised questions about the feasibility of the plan's centerpiece: a model called Coverage With Evidence With Development (CED), which critics fear could overburden providers, causing some to opt out of offering CAR T-cell treatment to Medicare patients. Others have asked about requirements to report patient-reported outcomes (PROs) and language they say could squeeze out community practices.

Finally, there are concerns that the plan's language is tightly crafted based on the first 2 CAR T-cell therapies approved by the FDA, without enough flexibility to reimburse providers for treatments in the research pipeline. CMS accepted comments on its proposed decision memo through March 17, 2019, and its final national coverage determination (NCD) is due May 17, 2019.[3]

Those who support CMS' approach say it addresses 2 knowledge gaps involving CAR T-cell therapy that are important to Medicare: the lack of data for treatment of those 65 years and older and the need to gather more information about PROs. This is the first year that the National Comprehensive Cancer Network (NCCN) has included a section on CAR T-cell–related toxicities in its guideline on Management of Immunotherapy-Related Toxicities,[4] and clinicians continue to fine-tune methods for preventing and treating the significant adverse events associated with CAR T-cell therapy, including cytokine release syndrome.

But providers who spoke with *Evidence-Based Oncology*™ (*EBO*) and have filed comments with CMS and appeared in public forums said these good intentions could have consequences if CMS' proposal isn't modified. Data gathering requirements include evidence for the CED model and reporting with specified PRO tools. An expert panel that discussed CMS' CAR T-cell reimbursement plan at the NCCN Annual Conference on March 21, 2019, said the losses cancer centers have already seen from CAR T-cell treatment are not sustainable, and some were unsure who would pay for data collection (see Sidebar). A comment letter sent to CMS from City of Hope in Duarte, California, which infused its first CAR T-cell trial patient in 2000, warned that the requirements "risk exacerbating patient access issues and compounding the financial losses that currently experience while serving Medicare beneficiaries."[1] (A signer of the letter, Joseph Alvarnas, MD, vice president for Government Affairs, is editor-in-chief of *EBO*.)

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At NCCN, Panel Featuring Payer Digs Into Reality of CAR T-cell Reimbursement

Mary Caffrey

Days after the March 17, 2019, comment deadline for CMS' plan to reimburse chimeric antigen receptor (CAR) T-cell therapy,[1] leading clinicians, a patient advocate, and the payer that triggered the process laid bare the truth of what's happening with this therapy: It may be saving lives, but leading cancer centers are losing money on Medicare patients, and that's not sustainable.

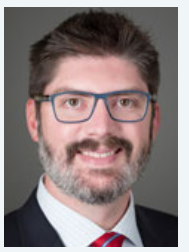
The panel discussion during the first day of the 2019 National Comprehensive Cancer Network (NCCN) Annual Meeting, held in Orlando, Florida, CAR T-cell therapy was the centerpiece for the broader problem with innovative cancer treatments. As moderator Clifford Goodman, PhD, of the Lewin Group, described it, complex therapies with new mechanisms of action, "are prompting, necessarily, a change in how we pay for this stuff."

So far, the old way of paying for treatment, Medicare in particular, has not kept pace. An early value-based agreement between Medicare and Novartis to cover the cost of the first approved treatment was scrapped,[2] and following a request from UnitedHealthcare, CMS embarked on the process to issue a National Coverage Determination (NCD), which would set reimbursement policy for CAR T-cell therapy across the country.[3]

SWEETENHAM

The centerpiece of that policy, Coverage With Evidence Development,[4] requires that patients be enrolled in studies or registries so that Medicare can gather data on how this therapy affects the population over 65 years. Panelist John W. Sweetenham, MD, of the Huntsman Cancer Institute at the University of Utah, saw merit in this idea. Others question whether the data-gathering requirements will burden cancer centers to the point that they opt out of caring for Medicare patients (see **Cover Story**).

Clinicians on the panel agreed that cancer centers cannot lose money indefinitely on treatment processes that cost 6 figures just for the therapy alone: $475,000 for tisagenlecleucel (Kymriah) in the pediatric acute lymphoblastic leukemia indication and $373,000 for that drug and axicabtagene ciloleucel (Yescarta) in diffuse large B-cell lymphoma.[5] Goodman's poll of the panel put the total cost of treatment between $800,000 and $1.5 million, but Frederick L. Locke, MD, of Moffitt Cancer Center, who presented a case involving a patient from the ZUMA-1 trial,[6] said Medicare's hospital billing codes were not designed for the care required to administer a therapy like CAR T, which brings significant adverse effects (AEs). Moffitt has designed an extensive patient and caregiver education program to prepare the families for what to expect.



LOCKE

Before the NCD process began, Florida was making progress in reimbursement with its regional Medicare Administrative Contractor (MAC), Locke said. As it exists today, "The process of paying for it doesn't allow Medicare to reimburse enough for hospitals to pay the therapy," he said "How is that going to work? We can only do this for so long where we're not getting fully paid."

"If it's not figured out soon," he warned, "we will not be able to do this for Medicare patients."

Impetus for the NCD Process

Goodman waited a bit to bring Jennifer Malin, MD, PhD, senior medical director of oncology and genetics for UnitedHealth Group, into the conversation. UnitedHealth Group's letter requesting an NCD prompted CMS to start the process,[3] and Goodman asked her to explain the thinking. He noted the letter did not mention cost. Malin explained while that is true,

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Even NCCN, which supports the concept of enrolling patients in registries, urged CMS to be mindful of the current financial burdens on cancer centers. In his comment, NCCN Chief Executive Officer Robert W. Carlson, MD, wrote, "NCCN firmly agrees with the principles of the registry.… We recommend that implementation of registry and data-collection be enacted with considerable focus on reducing administrative burden and supporting patient access to innovation.

"While NCCN recognizes that coverage determinations are made separate and apart from reimbursement determinations, we feel it is important that CMS implement the CED with an appreciation of the current reimbursement environment. Given that most providers of CAR T-cell therapy are currently being undercompensated by several hundreds of thousands of dollars for each Medicare patient treated, and possibly more if complications arise, NCCN has concern that an overly onerous CED process could lead providers to not participate due to the additional administrative cost."[1]

The National Coverage Analysis Process

In August 2017, the FDA approved the first CAR T-cell therapy, tisagenlecleucel (Kymriah), and CMS simultaneously announced a value-based agreement with sponsor Novartis that oncologists described as "you're only charged if you respond in 30 days."[5] The FDA approved the second therapy, axicabtagene ciloleucel (Yescarta), in October 2017. The treatments cost either $373,000 or $495,000, depending on indication.[6]

Early on, cancer centers focused on getting billing codes and finding out which state Medicaid programs would cover tisagenlecleucel when indicated for pediatric acute lymphoblastic leukemia.[6]

But UnitedHealthcare brought this to a halt with a request for an NCA; during the recent NCCN conference, UnitedHealthcare Senior Medical Director of Oncology and Genetics Jennifer Malin, MD, PhD, said the company needed consistency nationwide. That process included an August 2018 meeting of the Medicare Evidence Development & Coverage Advisory Commission to determine whether CMS would measure PROs as part of reimbursement;[7] this led to the inclusion of 2 measurement tools in the February 2019 proposed decision memo despite industry objections.

In the meantime, cancer centers that administer CAR T-cell therapy have been in limbo. With no Medicare national coverage policy in place, they have been using an existing billing code plus an add-on technology payment that does not come close to covering the cost of the manufactured cells; because of the lack of consistency between Medicare Administrative Contractors, oncologists in some states say Medicare basically doesn't pay for the engineered cells. In parts of the country, Medicaid patients who would benefit from treatment cannot gain access.

Features of the proposed reimbursement plan include[3]:

- The NCD would have highly specific criteria for what types of institutions can

continued

CAR T-CELL REIMBURSEMENT CONTINUED FROM PREVIOUS PAGE

traditional commercial contracts don't pay manufacturers. They pay providers based on a percentage of therapy cost, and that will not work with CAR T-cell therapy.

MALIN

Malin said UnitedHealth was motivated by the unique nature of the therapy and the questions that would arise if the regional MACs came to different decisions. What if a patient from Texas went to Moffitt in Florida for care?

A bigger issue was the prediction that CAR T-cell therapy would quickly expand beyond its approved uses, and cancer centers would want to use it off label, with justification. As a national payer, UnitedHealth felt it needed an NCD to address this. "How we do ensure it is consistently applied?" Malin asked. "As a national health plan, we don't want to see inequities based on where [people] live."

"That is why we're still in the midst of an inflection point," Goodman replied, explaining that many do not realize that reimbursement decisions are often made at the level of the MACs, not Medicare. For a pharmaceutical company, an NCD can be "risky business," he said. If the answer is "no," it's no everywhere, but if it's "yes," then its yes everywhere, Goodman explained. And that's the process that CAR T-cell therapy has been going through over the past year.

The Importance of PROs

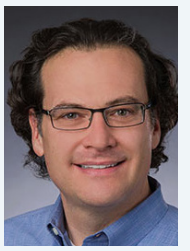
An August 2018 meeting of the Medicare Evidence Development and Coverage Advisory Committee examined the role of patient-reported outcomes (PROs)[7] and how they should factor into the reimbursement process. Some pharmaceutical companies felt this was inappropriate given the nature of CAR T-cell therapy, which can bring a debilitating wave of cytokine release syndrome and cognitive effects before they give way to patients getting back to the point of returning to work.

Said Malin, "We want to make sure patients are not just surviving but thriving."

Patient advocate and cancer survivor Stephanie Joho agreed that PROs are essential, even going a step further, saying that patients in clinical trials must be viewed as "coinvestigators," because sometimes the AEs patients think are important are overlooked. These could be important in 10 to 20 years, she said.

Sweetenham added, "Don't underestimate the importance of PROs," as they not only indicate quality of life but may also predict survival.

Lalan Wilfong, MD, of Texas Oncology, said the financial challenges that others described become even trickier in community practice, because revenue sources, like grant funding, are often unavailable. As CAR T-cell therapy moves to the community setting, a challenge will be educating physicians about the AEs that patients experience. Working with patients with high deductible plans is always a challenge—January is always a stressful month, he said—and community practices become experts in navigating these hurdles with their patients.



WILFONG

Just where to keep a CAR T-cell treatment in a community practice, because of its cost, has been a topic of discussion, given the buy-and-bill business model. "It will be interesting to see what happens if a drug that expensive becomes available."

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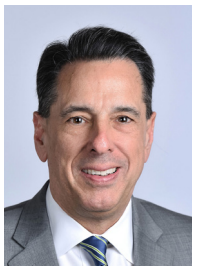
be reimbursed for CAR T-cell therapy; these criteria include staff they must employ. In comments filed with CMS, the Community Oncology Alliance (COA) said the use of the word *hospital* throughout the document could prevent member practices from receiving Medicare reimbursement.[2,3]

- The plan outlines what information must be tracked, based on whether the person receives therapy as an inpatient or an outpatient.
- The plan specifies measurement tools that must be used to report PROs and at what intervals over 2 years. A comment from MD Anderson Cancer Center said that tying reporting PROs to reimbursement is questionable, as patients often "come to CAR T providers for treatment and then return to [the] referring facility immediately after treatment completion."[1] In their letter, City of Hope leaders said that requiring either the National Institutes of Health Patient-Reported Outcomes Measurement Information System or the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events creates costs for institutions and "creates additional demands upon those patients who have undergone these treatments."[1]
- Repeat treatments will not be funded unless a new primary cancer is diagnosed.
- The "furnishing hospital" treating patients must accept "all manufactured products."

Balancing Need for Evidence With Burdens

Ted Okon, MBA, executive director of COA, told *EBO* in an interview last month that it appears CMS created the proposal to address a lack of data on how CAR T-cell therapy works in the Medicare population. But who should pay to gather these data? During the NCCN panel, Malin suggested the cost should be borne by the pharmaceutical companies. In their letter, City of Hope officials expressed concern that without clarity, the costs will fall on cancer centers.[1]

Representatives for the Biotechnology Innovation Organization (BIO), a trade group for the biotechnology industry, told *EBO* in an interview that its



OKON

members are also concerned that the proposal is written based on how CAR T-cell therapies are being used at the moment, not how they might be used in the future. City of Hope leaders concurred in their letter: "There are numerous CAR T-cell products that are in development that are differentiated from the 2 currently FDA-approved products. These emerging therapeutics may employ a different method of action or represent effector cell populations that are targeted against cancer types other than those targeted by Kymriah and Yescarta."[1]

In an interview with *EBO*, Mallory O'Connor, BIO's director of healthcare policy and federal programs, said the group shares COA's concern about language that could exclude community practices from reimbursement and seeks additional changes:

- The February 15, 2019, proposal states that CMS will pay for CAR T-cell therapy only in relapsed/refractory cancer, which reflects current FDA approvals. However, in the future, CAR T-cell or similar therapies may be used as the initial treatment for certain cancers. Already, discussions during the 2018 American Society of Clinical Oncology annual meeting have suggested the therapy may be more successful (and cost-effective) if patients' immune systems are not weakened by prior rounds of treatment.[8]
- There is a great need to clarify implementation dates and requirements and whether this NCD will serve as a model for treatments similar to CAR T-cell therapy.
- Other than many technical questions around the reporting requirements, BIO has asked about privacy issues: What if a patient needs treatment but does not want to share their data in a clinical trial or a registry?

Those who administer CAR T-cell therapy noted CMS' goal is to increase access to treatment, which is what Administrator Seema Verma said in unveiling the February plan. "CAR T-cell therapy was the first FDA-approved gene therapy, marking the beginning of an entirely new approach to treating serious and even life-threatening diseases," she said in a statement. The proposed coverage decision "would improve access to this therapy while deepening CMS' understanding of how patients in Medicare respond to it, so the agency can ensure that it is paying for CAR T-cell therapy for cases in which the benefits outweigh the risks."[9] ◆

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Fulphila®
(pegfilgrastim-jmdb) injection

The First FDA-approved Biosimilar for Neulasta® (pegfilgrastim)

INDICATION

Fulphila® is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Fulphila® is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

IMPORTANT SAFETY INFORMATION

Do not administer Fulphila® to patients with a history of serious allergic reactions, including anaphylaxis, to pegfilgrastim or filgrastim.

Splenic rupture, including fatal cases, can occur following the administration of pegfilgrastim products. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Fulphila®.

Acute respiratory distress syndrome (ARDS) can occur in patients receiving pegfilgrastim products. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Fulphila® for ARDS. Discontinue Fulphila® in patients with ARDS.

Serious allergic reactions, including anaphylaxis, can occur in patients receiving pegfilgrastim products. The majority of reported events occurred upon initial exposure and can recur within days after discontinuation of initial anti-allergic treatment. Permanently discontinue Fulphila® in patients with serious allergic reactions to any pegfilgrastim or filgrastim products.

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving pegfilgrastim products. Discontinue if sickle cell crisis occurs.

Glomerulonephritis has been reported in patients receiving pegfilgrastim products. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after withdrawal of pegfilgrastim products. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of Fulphila®.

White blood cell counts of 100 x 10^9/L or greater have been observed in patients receiving pegfilgrastim products. Monitoring of CBCs during therapy with Fulphila® is recommended.

Capillary leak syndrome has been reported after granulocyte colony-stimulating factor (G-CSF) administration, including pegfilgrastim products, and is characterized by hypotension, hypoalbuminemia, edema, and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

The G-CSF receptor, through which pegfilgrastim and filgrastim products act, has been found on tumor cell lines. The possibility that pegfilgrastim products act as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim products are not approved, cannot be excluded.

Aortitis has been reported in patients receiving pegfilgrastim products. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers (e.g., c-reactive protein and white blood cell count). Consider aortitis in patients who develop these signs and symptoms without known etiology and discontinue Fulphila® if aortitis is suspected.

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone imaging results.

The most common adverse reactions (≥ 5% difference in incidence) in placebo-controlled clinical trials are bone pain and pain in extremity.

Mylan®

FULPHILA® (pegfilgrastim-jmdb) injection, for subcutaneous use

Initial U.S. Approval: 2018

Brief summary. See package insert or full prescribing information.

INDICATIONS AND USAGE

Patients with Cancer Receiving Myelosuppressive Chemotherapy

Fulphila is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia *[see Clinical Studies]*.

Limitations of Use

Fulphila is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

CONTRAINDICATIONS

Fulphila is contraindicated in patients with a history of serious allergic reactions to pegfilgrastim products or filgrastim products *[see Warnings and Precautions]*. Reactions have included anaphylaxis *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Splenic Rupture

Splenic rupture, including fatal cases, can occur following the administration of pegfilgrastim products. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Fulphila.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) can occur in patients receiving pegfilgrastim products. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Fulphila, for ARDS. Discontinue Fulphila in patients with ARDS.

Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, can occur in patients receiving pegfilgrastim products. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Fulphila in patients with serious allergic reactions. Do not administer Fulphila to patients with a history of serious allergic reactions to pegfilgrastim products or filgrastim products.

Use in Patients with Sickle Cell Disorders

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving pegfilgrastim products. Discontinue Fulphila if sickle cell crisis occurs.

Glomerulonephritis

Glomerulonephritis has occurred in patients receiving pegfilgrastim products. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of pegfilgrastim products. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dosereduction or interruption of Fulphila.

Leukocytosis

White blood cell (WBC) counts of 100 x 10^9/L or greater have been observed in patients receiving pegfilgrastim products. Monitoring of complete blood count (CBC) during pegfilgrastim therapy is recommended.

Capillary Leak Syndrome

Capillary leak syndrome has been reported after G-CSF administration, including pegfilgrastim products, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte colony-stimulating factor (G-CSF) receptor through which pegfilgrastim products and filgrastim products act has been found on tumor cell lines. The possibility that pegfilgrastim products act as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim products are not approved, cannot be excluded.

Aortitis

Aortitis has been reported in patients receiving pegfilgrastim products. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers (e.g., c-reactive protein and white blood cell count). Consider aortitis in patients who develop these signs and symptoms without known etiology. Discontinue Fulphila if aortitis is suspected.

Nuclear Imaging

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone imaging results.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Splenic Rupture *[See Warnings and Precautions]*
- Acute Respiratory Distress Syndrome *[See Warnings and Precautions]*
- Serious Allergic Reactions *[See Warnings and Precautions]*
- Use in Patients with Sickle Cell Disorders *[See Warnings and Precautions]*
- Glomerulonephritis *[See Warnings and Precautions]*
- Leukocytosis *[See Warnings and Precautions]*
- Capillary Leak Syndrome *[See Warnings and Precautions]*
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells *[See Warnings and Precautions]*
- Aortitis *[see Warnings and Precautions]*

Clinical Trials Experience

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

Pegfilgrastim clinical trials safety data are based upon 932 patients receiving pegfilgrastim in seven randomized clinical trials. The population was 21 to 88 years of age and 92% female. The ethnicity was 75% Caucasian, 18% Hispanic, 5% Black, and 1% Asian. Patients with breast (n = 823), lung and thoracic tumors (n = 53) and lymphoma (n =56) received pegfilgrastim after nonmyeloablative cytotoxic chemotherapy. Most patients received a single 100 mcg/kg (n = 259) or a single 6 mg (n = 546) dose per chemotherapy cycle over 4 cycles.

The following adverse reaction data in Table 2 are from a randomized, double-blind, place-bo-controlled study in patients with metastatic or non-metastatic breast cancer receiving docetaxel 100 mg/m^2 every 21 days (Study 3). A total of 928 patients were randomized to receive either 6 mg pegfilgrastim (n = 467) or placebo (n = 461). The patients were 21 to 88 years of age and 99% female. The ethnicity was 66% Caucasian, 31% Hispanic, 2% Black, and < 1% Asian, Native American, or other.

The most common adverse reactions occurring in ≥ 5% of patients and with a between-group difference of ≥ 5% higher in the pegfilgrastim arm in placebo-controlled clinical trials are bone pain and pain in extremity.

Table 2. Adverse Reactions with ≥ 5% Higher Incidence in Pegfilgrastim Patients Compared to Placebo in Study 3

Body System Adverse Reaction	Placebo (N = 461)	Pegfilgrastim 6 mg SC on Day 2 (N = 467)
Musculoskeletal and connective tissue disorders		
Bone pain	26%	31%
Pain in extremity	4%	9%

Leukocytosis

In clinical studies, leukocytosis (WBC counts > 100 x 10^9/L) was observed in less than 1% of 932 patients with non-myeloid malignancies receiving pegfilgrastim. No complications attributable to leukocytosis were reported in clinical studies.

Immunogenicity

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

Binding antibodies to pegfilgrastim were detected using a BIAcore assay. The approximate limit of detection for this assay is 500 ng/mL. Pre-existing binding antibodies were detected in approximately 6% (51/849) of patients with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of pegfilgrastim products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Splenic rupture and splenomegaly (enlarged spleen) *[see Warnings and Precautions]*
- Acute respiratory distress syndrome (ARDS) *[see Warnings and Precautions]*
- Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, and urticaria, generalized erythema, and flushing *[see Warnings and Precautions]*
- Sickle cell crisis *[see Warnings and Precautions]*
- Glomerulonephritis *[see Warnings and Precautions]*
- Leukocytosis *[see Warnings and Precautions]*
- Capillary Leak Syndrome *[see Warnings and Precautions]*
- Injection site reactions
- Sweet's syndrome, (acute febrile neutrophilic dermatosis), cutaneous vasculitis
- Aortitis [*see Warnings and Precautions]*

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Although available data with Fulphila or pegfilgrastim product use in pregnant women are insufficient to establish whether there is a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes, there are available data from published studies in pregnant women exposed to filgrastim products. These studies have not established an association of filgrastim product use during pregnancy with major birth defects, miscarriage or adverse maternal or fetal outcomes.

In animal studies, no evidence of reproductive/developmental toxicity occurred in the offspring of pregnant rats that received cumulative doses of pegfilgrastim approximately 10 times the recommended human dose (based on body surface area). In pregnant rabbits, increased embryolethality and spontaneous abortions occurred at 4 times the maximum recommended human dose simultaneously with igns of maternal toxicity *(see Data)*.

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 2-4% and 15-20%, respectively.

Data

Human Data

Retrospective studies indicate that exposure to pegfilgrastim is without significant adverse effect on fetal outcomes and neutropenia. Preterm deliveries have been reported in some patients.

Animal Data

Pregnant rabbits were dosed with pegfilgrastim subcutaneously every other day during the period of organogenesis. At cumulative doses ranging from the approximate human dose to approximately 4 times the recommended human dose (based on body surface area), the treated rabbits exhibited decreased maternal food consumption, maternal weight loss, as well as reduced fetal body weights and delayed ossification of the fetal skull; however, no structural anomalies were observed in the offspring from either study. Increased incidences of post-implantation losses and spontaneous abortions (more than half the pregnancies) were observed at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose.

Three studies were conducted in pregnant rats dosed with pegfilgrastim at cumulative doses up to approximately 10 times the recommended human dose at the following stages of gestation: during the period of organogenesis, from mating through the first half of pregnancy, and from the first trimester through delivery and lactation. No evidence of fetal loss or structural malformations was observed in any study. Cumulative doses equivalent to approximately 3 and 10 times the recommended human dose resulted in transient evidence of wavy ribs in fetuses of treated mothers (detected at the end of gestation but no longer present in pups evaluated at the end of lactation).

Lactation

Risk Summary

There are no data on the presence of pegfilgrastim in human milk, the effects on the breastfed child, or the effects on milk production. Other filgrastim products are secreted poorly into breast milk, and filgrastim products are not absorbed orally by neonates. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Fulphila and any potential adverse effects on the breastfed child from Fulphila or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of pegfilgrastim have been established in pediatric patients. No overall differences in safety were identified between adult and pediatric patients based on postmarketing surveillance and review of the scientific literature. Use of pegfilgrastim in pediatric patients for chemotherapy-induced neutropenia is based on adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients with sarcoma *[see Clinical Pharmacology and Clinical Studies]*.

Geriatric Use

Of the 932 patients with cancer who received pegfilgrastim in clinical studies, 139 (15%) were aged 65 and over, and 18 (2%) were aged 75 and over. No overall differences in safety or effectiveness were observed between patients aged 65 and older and younger patients.

OVERDOSAGE

Overdosage of pegfilgrastim products may result in leukocytosis and bone pain. Events of edema, dyspnea, and pleural effusion have been reported in a single patient who administered pegfilgrastim on 8 consecutive days in error. In the event of overdose, the patient should be monitored for adverse reactions *[see Adverse Reactions]*.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenesis studies have been performed with pegfilgrastim products.

Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 6 to 9 times higher than the recommended human dose (based on body surface area).

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Advise patients of the following risks and potential risks with Fulphila:

- Splenic rupture and splenomegaly
- Acute Respiratory Distress Syndrome
- Serious allergic reactions
- Sickle cell crisis
- Glomerulonephritis
- Capillary Leak Syndrome
- Aortitis

Instruct patients who self-administer Fulphila using the single-dose prefilled syringe of the:

- Importance of following the Instructions for Use.
- Dangers of reusing syringes.
- Importance of following local requirements for proper disposal of used syringes.

Mylan®

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