SPECIAL ISSUE: PHARMACISTS IN CANCER CARE

1995 • 2017 22 YEARS RESEARCH & LEADERSHIP

AJMC®
THE AMERICAN JOURNAL OF MANAGED CARE®

Evidence-Based ONCOLOGY™

OCTOBER 2017
VOL. 23 • NO. 12

ALSO IN THIS ISSUE

FORMULARY DECISIONS

Formulary Considerations: The Past, Present, and Future

Molly Billstein Leber, PharmD, BCPS, FASHP

IN THE 1940s, when health system formularies were created, they were simply a current list of medications stocked in the pharmacy, along with some related information about each drug.[1] In the 1980s, the clinical and economic value of well-controlled and managed formularies were highlighted.[2] Today, Pharmacy and Therapeutic (P&T) committees are considered a critical tool for healthcare organizations to ensure safe, appropriate, and cost-effective use of pharmaceuticals for patient care. A guideline on P&T committees and formulary systems, developed by the American Society of Health-System Pharmacists, summarizes the best practices and techniques that should be implemented for optimal formulary system management.[1] Policies and procedures for procuring, dispensing, administering, and appropriate utilization of medications are also included in the formulary management process.

Pharmacy and Therapeutic committees play a vital role in ensuring safe, appropriate, and cost-effective use of pharmaceuticals for patients.

To promote evidence-based medicine, there must be a systematic approach to the evaluation of biomedical literature and its application to clinical practice, which should be applied to formulary decision making.[1] This often goes beyond the FDA approval process. The most important decision at hand for a P&T committee is the definition of a formulary drug. Typically, formulary agents are deemed urgent or used with sufficient frequency that they are stocked in the pharmacy in appropriate quantities to ensure patients have sufficient access to safe, efficacious, and cost-efficient drugs.

CONTINUED ON SP490

COMMUNITY PHARMACY

PBMs: Their Role, the Problems, and How Practices Can Work With Them

Ray Bailey, RPh, and Ricky Newton, CPA

THE RELATIONSHIP BETWEEN PHARMACY benefit managers (PBMs) and community oncologists has not been an easy one. With the increasing prevalence of oral oncolytics, PBMs and community oncologists have seen a concurrent increase in their mutual interaction. Each can rail against the other, claiming better, faster, and more cost-effective care, or community oncologists can find a way to co-exist with and manage PBMs in a manner that would benefit patients and their practice.

The Role of PBMs in Cancer Care

In many areas of medicine, the role of PBMs is established. PBMs can be a beneficial part of the patient care team, especially for chronic conditions such as hyperlipidemia, hyperglycemia, and hypertension. However, the role of PBMs in cancer care is less clear. For acute, severe, and often life-threatening conditions like cancer, the community oncologist is better able to provide the intense, rapid-response, personalized, and familiar care that is necessary.

CONTINUED ON SP497

QUALITY DISPENSING

Positive Quality Interventions: An Innovative Platform for Oncology Practice Collaboration

Joshua Nubla, PharmD; Neal Dave, PharmD; and Michael Reff, RPh, MBA

CARE FOR PATIENTS IN THE ONCOLOGY setting is extremely diverse and complex. Management of the many distinct oral oncolytic regimens through pharmacy dispensing platforms in clinical practice can leave gaps within the healthcare system that should be addressed. These gaps are not caused by knowledge gaps; they result from a lack of contact

CONTINUED ON SP500

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The Institute for Value-Based Medicine®

COA Community Oncology Alliance

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

KYPROLIS® (carfilzomib) is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

IMPORTANT SAFETY INFORMATION

Cardiac Toxicities: New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of KYPROLIS. Some events occurred in patients with normal baseline ventricular function. Death due to cardiac arrest has occurred within one day of KYPROLIS administration.

- Monitor patients for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold KYPROLIS for Grade 3 or 4 cardiac adverse events until recovery, and consider whether to restart KYPROLIS at 1 dose level reduction based on a benefit/risk assessment.
- While adequate hydration is required prior to each dose in Cycle 1, monitor all patients for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate in patients with baseline cardiac failure or who are at risk for cardiac failure.
- Patients ≥ 75 years, the risk of cardiac failure is increased. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias may be at greater risk for cardiac complications and should have a comprehensive medical assessment (including blood pressure and fluid management) prior to starting treatment with KYPROLIS and remain under close follow-up.

Acute Renal Failure: Cases of acute renal failure and renal insufficiency adverse events (including renal failure) have occurred in patients receiving KYPROLIS. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received KYPROLIS monotherapy. Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

Tumor Lysis Syndrome: Cases of Tumor Lysis Syndrome (TLS), including fatal outcomes, have occurred in patients receiving KYPROLIS. Patients with multiple myeloma and a high tumor burden should be considered at greater risk for TLS. Adequate hydration is required prior to each dose in Cycle 1, and in subsequent cycles as needed. Consider uric acid lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly. Withhold KYPROLIS until TLS is resolved.

Pulmonary Toxicity: Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in patients receiving KYPROLIS. Some events have been fatal. In the event of drug-induced pulmonary toxicity, discontinue KYPROLIS.

Pulmonary Hypertension: Pulmonary arterial hypertension (PAH) was reported in patients treated with KYPROLIS. Evaluate with cardiac imaging and/or other tests as indicated. Withhold KYPROLIS for PAH until resolved or returned to baseline and consider whether to restart KYPROLIS based on a benefit/risk assessment.

Dyspnea: Dyspnea was reported in patients treated with KYPROLIS. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop KYPROLIS for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart KYPROLIS based on a benefit/risk assessment.

Hypertension: Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with KYPROLIS. Some of these events have been fatal. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold KYPROLIS and evaluate. Consider whether to restart KYPROLIS based on a benefit/risk assessment.

Venous Thrombosis: Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with KYPROLIS. Thromboprophylaxis is recommended for patients being treated with the combination of KYPROLIS with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.

- Patients using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment with KYPROLIS in combination with dexamethasone or lenalidomide plus dexamethasone.

Infusion Reactions: Infusion reactions, including life-threatening reactions, have occurred in patients receiving KYPROLIS. Symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of KYPROLIS. Premedicate with dexamethasone to reduce the incidence and severity of infusion reactions. Inform patients of the risk and of symptoms of an infusion reaction and to contact a physician immediately if they occur.

Hemorrhage: Fatal or serious cases of hemorrhage have been reported in patients receiving KYPROLIS. Hemorrhagic events have included gastrointestinal, pulmonary, and intracranial hemorrhage and epistaxis. Promptly evaluate signs and symptoms of blood loss. Reduce or withhold dose as appropriate.

Thrombocytopenia: KYPROLIS causes thrombocytopenia with recovery to baseline platelet count usually by the start of the next cycle. Thrombocytopenia was reported in patients receiving KYPROLIS. Monitor platelet counts frequently during treatment with KYPROLIS. Reduce or withhold dose as appropriate.

Hepatic Toxicity and Hepatic Failure: Cases of hepatic failure, including fatal cases, have been reported during treatment with KYPROLIS. KYPROLIS can cause increased serum transaminases. Monitor liver enzymes regularly regardless of baseline values. Reduce or withhold dose as appropriate.

Thrombotic Microangiopathy: Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), including fatal outcome have occurred in patients receiving KYPROLIS. Monitor for signs and symptoms of TTP/HUS. Discontinue KYPROLIS if diagnosis is suspected. If the diagnosis of TTP/HUS is excluded, KYPROLIS may be restarted. The safety of reinitiating KYPROLIS therapy in patients previously experiencing TTP/HUS is not known.

Posterior Reversible Encephalopathy Syndrome (PRES): Cases of PRES have occurred in patients receiving KYPROLIS. PRES was formerly known as Reversible Posterior Leukoencephalopathy Syndrome. Consider a neuro-radiological imaging (MRI) for onset of visual or neurological symptoms. Discontinue KYPROLIS if PRES is suspected and evaluate. The safety of reinitiating KYPROLIS therapy in patients previously experiencing PRES is not known.

Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-ineligible Patients: In a clinical trial of transplant-ineligible patients with newly diagnosed multiple myeloma comparing KYPROLIS, melphalan, and prednisone (KMP) vs bortezomib, melphalan, and prednisone (VMP), a higher incidence of serious and fatal adverse events was observed in patients in the KMP arm. KYPROLIS in combination with melphalan and prednisone is not indicated for transplant-ineligible patients with newly diagnosed multiple myeloma.

Embryo-fetal Toxicity: KYPROLIS can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals.

- Females of reproductive potential should be advised to avoid becoming pregnant while being treated with KYPROLIS. Males of reproductive potential should be advised to avoid fathering a child while being treated with KYPROLIS. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the fetus.

ADVERSE REACTIONS

The most common adverse reactions occurring in at least 20% of patients treated with KYPROLIS in the combination therapy trials: anemia, neutropenia, diarrhea, dyspnea, fatigue, thrombocytopenia, pyrexia, insomnia, muscle spasm, cough, upper respiratory tract infection, hypokalemia.

Please see Brief Summary of full Prescribing Information on adjacent pages.

Now With Overall Survival Data

WHEN MULTIPLE MYELOMA RELAPSES,

Don't put your patient's survival at risk

KYPROLIS®-based regimens (KRd and Kd) reduced the risk of death by 21% vs Rd and Vd and extended median overall survival by 7.9 and 7.6 months, respectively[1,2,*,†,‡,§]

KRd AS A TRIPLET THERAPY

8.7-month increase in median PFS[3]

26.3 months (KRd) vs 17.6 months (Rd); hazard ratio (KRd/Rd) = 0.69 (95% CI: 0.57-0.83); two-sided $P = 0.0001$

7.9-month increase in median OS[1]

***48.3 months (KRd) vs 40.4 months (Rd)**; hazard ratio (KRd/Rd) = 0.79 (95% CI: 0.67-0.95)

>3x CR or better[3]

32% (KRd) vs 9% (Rd)

†**KRd vs Rd Phase 3 design:** N = 792, randomized (1:1), open-label superiority study comparing KRd vs Rd in relapsed or refractory multiple myeloma patients who had received 1 to 3 lines of therapy. The primary endpoint was progression-free survival. Select secondary endpoints included overall survival and overall response rate. KYPROLIS® was discontinued per protocol in the KRd arm after 18 cycles of treatment.[3,4]

Kd AS A DOUBLET THERAPY

9.3-month increase in median PFS[3]

18.7 months (Kd) vs 9.4 months (Vd); hazard ratio (Kd/Vd) = 0.53 (95% CI: 0.44-0.65); one-sided $P < 0.0001$

7.6-month increase in median OS[2]

‡**47.6 months (Kd) vs 40.0 months (Vd)**; hazard ratio (Kd/Vd) = 0.79 (95% CI: 0.65-0.96); one-sided $P = 0.01$

§**Kd vs Vd Phase 3 design:** N = 929, randomized (1:1), open-label superiority study comparing Kd to Vd in relapsed or refractory multiple myeloma patients who had received 1 to 3 lines of therapy. The primary endpoint was progression-free survival. Overall survival was a prespecified key secondary efficacy endpoint.[3,5]

See more OS results at KYPROLIS-HCP.com

The significance level of the preplanned OS second interim analysis is determined by the O'Brien-Fleming type alpha spending function based on the number of OS events observed by the analysis time.[6,7]

The KRd vs Rd and Kd vs Vd OS results have not yet been reviewed by FDA, and inclusion in the final, FDA-approved label for KYPROLIS® has yet to be determined.

CI = confidence interval; CR = complete response; Kd = KYPROLIS® and dexamethasone; KRd = KYPROLIS®, lenalidomide, and dexamethasone; OS = overall survival; PFS = progression-free survival; Rd = lenalidomide and dexamethasone; Vd = VELCADE® (bortezomib) and dexamethasone.

IMPORTANT SAFETY INFORMATION

Cardiac Toxicities: New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of KYPROLIS. Some events occurred in patients with normal baseline ventricular function. Death due to cardiac arrest has occurred within one day of KYPROLIS administration.

Please see additional Important Safety Information on left.

References: 1. Data on file, Amgen; [1]; 2017. **2.** Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Overall survival of patients with relapsed or refractory multiple myeloma treated with carfilzomib and dexamethasone versus bortezomib and dexamethasone in the randomized phase 3 ENDEAVOR trial. Abstract presented at: 16th International Myeloma Workshop; March 1-4, 2017; New Delhi, India. Abstract. **3.** KYPROLIS® (carfilzomib) prescribing information, Onyx Pharmaceuticals Inc., an Amgen Inc. subsidiary. **4.** Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2015;372:142-152. **5.** Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol*. 2016;17:27-38. **6.** Data on file, Amgen; [2]; 2017. **7.** Data on file, Amgen; [3]; 2017.

VELCADE® is a registered trademark of Millennium Pharmaceuticals.

AMGEN®

Kyprolis™ (carfilzomib) for Injection

KYPROLIS® (carfilzomib) for injection, for intravenous use
Brief Summary of Prescribing Information.
Please see the KYPROLIS package insert for full prescribing information.

1. INDICATIONS AND USAGE

- Kyprolis is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.
- Kyprolis is indicated as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.

5. WARNINGS AND PRECAUTIONS

5.1 Cardiac Toxicities

New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of Kyprolis. Some events occurred in patients with normal baseline ventricular function. In clinical studies with Kyprolis, these events occurred throughout the course of Kyprolis therapy. Death due to cardiac arrest has occurred within one day of Kyprolis administration. In a randomized, open-label, multicenter trial evaluating Kyprolis in combination with lenalidomide and dexamethasone (KRd) versus lenalidomide/dexamethasone (Rd), the incidence of cardiac failure events was 6% in the KRd arm versus 4% in the Rd arm. In a randomized, open-label, multicenter trial of Kyprolis plus dexamethasone (Kd) versus bortezomib plus dexamethasone (Vd), the incidence of cardiac failure events was 8% in the Kd arm versus 3% in the Vd arm.

Monitor patients for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold Kyprolis for Grade 3 or 4 cardiac adverse events until recovery, consider whether to restart Kyprolis at 1 dose level reduction based on a benefit/risk assessment.

While adequate hydration is required prior to each dose in Cycle 1, all patients should also be monitored for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate in patients with baseline cardiac failure or who are at risk for cardiac failure.

In patients ≥ 75 years of age, the risk of cardiac failure is increased compared to patients < 75 years of age. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications and should have a comprehensive medical assessment (including blood pressure and fluid management) prior to starting treatment with Kyprolis and remain under close follow-up.

5.2 Acute Renal Failure

Cases of acute renal failure have occurred in patients receiving Kyprolis. Renal insufficiency adverse events (including renal failure) have occurred in approximately 10% of patients treated with Kyprolis. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received Kyprolis monotherapy. This risk was greater in patients with a baseline reduced estimated creatinine clearance (calculated using Cockcroft and Gault equation). Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

5.3 Tumor Lysis Syndrome

Cases of tumor lysis syndrome (TLS), including fatal outcomes, have been reported in patients who received Kyprolis. Patients with multiple myeloma and a high tumor burden should be considered to be at greater risk for TLS. Ensure that patients are well hydrated before administration of Kyprolis in Cycle 1, and in subsequent cycles as needed. Consider uric acid-lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly, including interruption of Kyprolis until TLS is resolved.

5.4 Pulmonary Toxicity

Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in less than 1% of patients receiving Kyprolis. Some events have been fatal. In the event of drug-induced pulmonary toxicity, discontinue Kyprolis.

5.5 Pulmonary Hypertension

Pulmonary arterial hypertension was reported in approximately 1% of patients treated with Kyprolis and was Grade 3 or greater in less than 1% of patients. Evaluate with cardiac imaging and/or other tests as indicated. Withhold Kyprolis for pulmonary hypertension until resolved or returned to baseline, and consider whether to restart Kyprolis based on a benefit/risk assessment.

5.6 Dyspnea

Dyspnea was reported in 28% of patients treated with Kyprolis and was Grade 3 or greater in 4% of patients. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop Kyprolis for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart Kyprolis based on a benefit/risk assessment.

5.7 Hypertension

Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with Kyprolis. In a randomized, open-label, multicenter trial evaluating Kyprolis in combination with KRd versus Rd, the incidence of hypertension events was 16% in the KRd arm versus 8% in the Rd arm. In a randomized, open-label, multicenter trial of Kd versus Vd, the incidence of hypertension events was 26% in the Kd arm versus 10% in the Vd arm. Some of these events have been fatal. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold Kyprolis and evaluate. Consider whether to restart Kyprolis based on a benefit/risk assessment.

5.8 Venous Thrombosis

Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with Kyprolis. In a randomized, open-label, multicenter trial evaluating KRd versus Rd (with thromboprophylaxis used in both arms), the incidence of venous thromboembolic events in the first 12 cycles was 13% in the KRd arm versus 6% in the Rd arm. In a randomized, open-label, multicenter trial of Kd versus Vd, the incidence of venous thromboembolic events in months 1–6 was 9% in the Kd arm versus 2% in the Vd arm. With Kyprolis monotherapy, the incidence of venous thromboembolic events was 2%.

Thromboprophylaxis is recommended for patients being treated with the combination of Kyprolis with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.

Patients using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment with Kyprolis in combination with dexamethasone or lenalidomide plus dexamethasone.

5.9 Infusion Reactions

Infusion reactions, including life-threatening reactions, have occurred in patients receiving Kyprolis. Symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of Kyprolis. Administer dexamethasone prior to Kyprolis to reduce the incidence and severity of infusion reactions. Inform patients of the risk and of symptoms and to contact a physician immediately if symptoms of an infusion reaction occur.

5.10 Hemorrhage

Fatal or serious cases of hemorrhage have been reported in patients treated with Kyprolis. Hemorrhagic events have included gastrointestinal, pulmonary, and intracranial hemorrhage and epistaxis. The bleeding can be spontaneous, and intracranial hemorrhage has occurred without trauma. Hemorrhage has been reported in patients having either low or normal platelet counts. Hemorrhage has also been reported in patients who were not on antiplatelet therapy or anticoagulation. Promptly evaluate signs and symptoms of blood loss. Reduce or withhold dose as appropriate.

5.11 Thrombocytopenia

Kyprolis causes thrombocytopenia with platelet nadirs observed between Day 8 and Day 15 of each 28-day cycle, with recovery to baseline platelet count usually by the start of the next cycle. Thrombocytopenia was reported in approximately 40% of patients in clinical trials with Kyprolis. Monitor platelet counts frequently during treatment with Kyprolis. Reduce or withhold dose as appropriate. Hemorrhage may occur.

5.12 Hepatic Toxicity and Hepatic Failure

Cases of hepatic failure, including fatal cases, have been reported (< 1%) during treatment with Kyprolis. Kyprolis can cause increased serum transaminases. Monitor liver enzymes regularly, regardless of baseline values. Reduce or withhold dose as appropriate.

5.13 Thrombotic Microangiopathy

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received Kyprolis. Some of these events have been fatal. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop Kyprolis and evaluate. If the diagnosis of TTP/HUS is excluded, Kyprolis may be restarted. The safety of reinitiating Kyprolis therapy in patients previously experiencing TTP/HUS is not known.

5.14 Posterior Reversible Encephalopathy Syndrome

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving Kyprolis. PRES, formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS), is a neurological disorder which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension, and the diagnosis is confirmed by neuro-radiological imaging (MRI). Discontinue Kyprolis if PRES is suspected and evaluate. The safety of reinitiating Kyprolis therapy in patients previously experiencing PRES is not known.

5.15 Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Patients

In a clinical trial of 955 transplant-ineligible patients with newly diagnosed multiple myeloma randomized to Kyprolis (20/36 mg/m^2 by 30-minute infusion twice weekly for four of each six-week cycle), melphalan, and prednisone (KMP) or bortezomib, melphalan, and prednisone (VMP), a higher incidence of fatal adverse reactions (7% versus 4%) and serious adverse reactions (50% versus 42%) were observed in the KMP arm compared to patients in the VMP arm, respectively. Patients in the KMP arm were observed to have a higher incidence of any grade adverse reactions involving cardiac failure (11% versus 4%), hypertension (25% versus 8%), acute renal failure (14% versus 6%), and dyspnea (18% versus 9%). This study did not meet its primary outcome measure of superiority in progression-free survival for the KMP arm. Kyprolis in combination with melphalan and prednisone is not indicated for transplant-ineligible patients with newly diagnosed multiple myeloma.

5.16 Embryo-Fetal Toxicity

Kyprolis can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using Kyprolis.

Advise females of reproductive potential to avoid becoming pregnant while being treated with Kyprolis. Advise males of reproductive potential to avoid fathering a child while being treated with Kyprolis. Advise women who use Kyprolis during pregnancy or become pregnant during treatment with Kyprolis of the potential hazard to the fetus.

6. ADVERSE REACTIONS

The following adverse reactions have been discussed above and can be found in the Warnings and Precautions section of the prescribing information. They include Cardiac Toxicities, Acute Renal Failure, TLS, Pulmonary Toxicity, Pulmonary Hypertension, Dyspnea, Hypertension, Venous Thrombosis, Infusion Reactions, Hemorrhage, Thrombocytopenia, Hepatic Toxicity and Hepatic Failure, Thrombotic Microangiopathy, PRES, and Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Patients.

6.1 Clinical Trials Experience

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

Safety Experience with Kyprolis in Combination with Lenalidomide and Dexamethasone in Patients with Multiple Myeloma

The safety of Kyprolis in combination with lenalidomide and dexamethasone (KRd) was evaluated in an open-label randomized study in patients with relapsed multiple myeloma. The median number of cycles initiated was 22 cycles for the KRd arm and 14 cycles for the Rd arm.

Deaths due to adverse reactions within 30 days of the last dose of any therapy in the KRd arm occurred in 27/392 (7%) patients compared with 27/389 (7%) patients who died due to adverse reactions within 30 days of the last dose of any Rd therapy. The most common cause of deaths occurring in patients (%) in the two arms (KRd versus Rd) included cardiac 10 (3%) versus 7 (2%), infection 9 (2%) versus 10 (3%), renal 0 (0%) versus 1 (< 1%), and other adverse reactions 9 (2%) versus 10 (3%). Serious adverse reactions were reported in 60% of the patients in the KRd arm and 54% of the patients in the Rd arm. The most common serious adverse reactions reported in the KRd arm as compared with the Rd arm were pneumonia (14% vs. 11%), respiratory tract infection (4% vs. 1.5%), pyrexia (4% vs. 2%), and pulmonary embolism (3% vs. 2%). Discontinuation due to any adverse reaction occurred in 26% in the KRd arm versus 25% in the Rd arm. Adverse reactions leading to discontinuation of Kyprolis occurred in 12% of patients and the most common reactions included pneumonia (1%), myocardial infarction (0.8%), and upper respiratory tract infection (0.8%).

Most Common Adverse Reactions (≥ 10% in the KRd Arm) Occurring in Cycles 1–12 (20/27 mg/m^2 Regimen in Combination with Lenalidomide and Dexamethasone)

	KRd Arm (N = 392), n (%)		Rd Arm (N = 389), n (%)	
Adverse Reactions by Body System	**Any Grade**	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**
Blood and Lymphatic System Disorders				
Anemia	138 (35)	53 (14)	127 (33)	47 (12)
Neutropenia	124 (32)	104 (27)	115 (30)	89 (23)
Thrombocytopenia	100 (26)	58 (15)	75 (19)	39 (10)
Gastrointestinal Disorders				
Diarrhea	115 (29)	7 (2)	105 (27)	12 (3)
Constipation	68 (17)	0	53 (14)	1 (0)
Nausea	60 (15)	1 (0)	39 (10)	3 (1)
General Disorders and Administration Site Conditions				
Fatigue	109 (28)	21 (5)	104 (27)	20 (5)
Pyrexia	93 (24)	5 (1)	64 (17)	1 (0)
Edema peripheral	63 (16)	2 (1)	57 (15)	2 (1)
Asthenia	53 (14)	11 (3)	46 (12)	7 (2)
Infections and Infestations				
Upper respiratory tract infection	85 (22)	7 (2)	52 (13)	3 (1)

Nasopharyngitis	63 (16)	0	43 (11)	0
Bronchitis	54 (14)	5 (1)	39 (10)	2 (1)
Pneumonia[a]	54 (14)	35 (9)	43 (11)	27 (7)
Metabolism and Nutrition Disorders				
Hypokalemia	78 (20)	22 (6)	35 (9)	12 (3)
Hypocalcemia	55 (14)	10 (3)	39 (10)	5 (1)
Hyperglycemia	43 (11)	18 (5)	33 (9)	15 (4)
Musculoskeletal and Connective Tissue Disorders				
Muscle spasms	88 (22)	3 (1)	73 (19)	3 (1)
Nervous System Disorders				
Peripheral neuropathies[b]	43 (11)	7 (2)	37 (10)	4 (1)
Psychiatric Disorders				
Insomnia	63 (16)	6 (2)	50 (13)	8 (2)
Respiratory, Thoracic, and Mediastinal Disorders				
Cough[c]	91 (23)	2 (1)	52 (13)	0
Dyspnea[d]	70 (18)	9 (2)	58 (15)	6 (2)
Skin and Subcutaneous Tissue Disorders				
Rash	45 (12)	5 (1)	53 (14)	5 (1)
Vascular Disorders				
Embolic and thrombotic events venous[e]	49 (13)	16 (4)	22 (6)	9 (2)
Hypertension[f]	41 (11)	12 (3)	15 (4)	4 (1)

KRd = Kyprolis, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone.

[a] Pneumonia includes pneumonia and bronchopneumonia.

[b] Peripheral neuropathies includes peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.

[c] Cough includes cough and productive cough.

[d] Dyspnea includes dyspnea and dyspnea exertional.

[e] Embolic and thrombotic events, venous include deep vein thrombosis, pulmonary embolism, thrombophlebitis superficial, thrombophlebitis, venous thrombosis limb, post thrombotic syndrome, venous thrombosis.

[f] Hypertension includes hypertension, hypertensive crisis.

There were 274 (70%) patients in the KRd arm who received treatment beyond Cycle 12. There were no new clinically relevant adverse reactions that emerged in the later treatment cycles.

Grade 3 and higher adverse reactions that occurred during Cycles 1–12 with a substantial difference (≥ 2%) between the two arms were neutropenia, thrombocytopenia, hypokalemia, and hypophosphatemia.

Safety Experience with Kyprolis in Combination with Dexamethasone in Patients with Multiple Myeloma

The safety of Kyprolis in combination with dexamethasone was evaluated in an open-label, randomized trial of patients with relapsed multiple myeloma. Patients received treatment for a median duration of 40 weeks in the Kyprolis/dexamethasone (Kd) arm and 27 weeks in the bortezomib/dexamethasone (Vd) arm. Deaths due to adverse reactions within 30 days of last study treatment occurred in 22/463 (5%) patients in the Kd arm and 21/456 (5%) patients in the Vd arm. The causes of death occurring in patients (%) in the two arms (Kd vs. Vd) included cardiac 7 (2%) versus 5 (1%), infections 5 (1%) versus 8 (2%), disease progression 6 (1%) versus 4 (1%), pulmonary 3 (1%) versus 2 (< 1%), renal 1 (< 1%) versus 0 (0%), and other adverse events 2 (< 1%) versus 2 (< 1%). Serious adverse reactions were reported in 48% of the patients in the Kd arm and 36% of the patients in the Vd arm. In both treatment arms, pneumonia was the most commonly reported serious adverse reaction (6% vs. 9%). Discontinuation due to any adverse reaction occurred in 20% in the Kd arm versus 21% in the Vd arm. The most common reaction leading to discontinuation was cardiac failure in the Kd arm (n = 6, 1.3%) and peripheral neuropathy in the Vd arm (n = 19, 4.2%).

Most Common Adverse Reactions (≥ 10% in the Kd Arm) Occurring in Months 1–6 (20/56 mg/m^2 Regimen in Combination with Dexamethasone)

	Kd (N = 463), n (%)		Vd (N = 456), n (%)	
Adverse Reaction by Body System	**Any Grade**	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**
Blood and Lymphatic System Disorders				
Anemia	160 (35)	57 (12)	112 (25)	43 (9)
Thrombocytopenia[a]	127 (27)	46 (10)	112 (25)	65 (14)
Gastrointestinal Disorders				
Diarrhea	111 (24)	14 (3)	150 (33)	26 (6)
Nausea	69 (15)	4 (1)	66 (15)	3 (1)
Constipation	58 (13)	1 (0)	109 (24)	6 (1)
Vomiting	45 (10)	5 (1)	32 (7)	3 (1)
General Disorders and Administration Site Conditions				
Fatigue	112 (24)	13 (3)	124 (27)	25 (6)
Pyrexia	102 (22)	9 (2)	52 (11)	3 (1)
Peripheral edema	75 (16)	3 (1)	73 (16)	3 (1)
Asthenia	71 (15)	9 (2)	66 (14)	13 (3)
Infections and Infestations				
Upper respiratory tract infection	66 (14)	4 (1)	54 (12)	3 (1)
Bronchitis	54 (12)	5 (1)	26 (6)	2 (0)
Nasopharyngitis	45 (10)	0 (0)	42 (9)	1 (0)
Musculoskeletal and Connective Tissue Disorders				
Muscle spasms	66 (14)	1 (0)	22 (5)	3 (1)
Back pain	58 (13)	7 (2)	60 (13)	8 (2)
Nervous System Disorders				
Headache	68 (15)	4 (1)	38 (8)	2 (0)
Peripheral neuropathies[b]	54 (12)	7 (2)	167 (37)	23 (5)
Psychiatric Disorders				
Insomnia	103 (22)	5 (1)	113 (25)	10 (2)
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea[c]	123 (27)	23 (5)	66 (15)	8 (2)
Cough[d]	91 (20)	0 (0)	61 (13)	2 (0)
Vascular Disorders				
Hypertension[e]	80 (17)	29 (6)	33 (7)	12 (3)

Kd = Kyprolis and dexamethasone; Vd = bortezomib and dexamethasone.

[a] Thrombocytopenia includes platelet count decreased and thrombocytopenia.

[b] Peripheral neuropathies include peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.

[c] Dyspnea includes dyspnea and dyspnea exertional.

[d] Cough includes cough and productive cough.

[e] Hypertension includes hypertension, hypertensive crisis, and hypertensive emergency.

The event rate of ≥ Grade 2 peripheral neuropathy in the Kd arm was 6% (95% CI: 4, 8) versus 32% (95% CI: 28, 36) in the Vd arm.

6.2 Postmarketing Experience

The following additional adverse reactions were reported in the postmarketing experience with Kyprolis. 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: hemolytic uremic syndrome (HUS), gastrointestinal perforation, pericarditis.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Kyprolis can cause fetal harm based on findings from animal studies and the drug's mechanism of action. There are no adequate and well-controlled studies in pregnant women using Kyprolis.

Females of reproductive potential should be advised to avoid becoming pregnant while being treated with Kyprolis. Males of reproductive potential should be advised to avoid fathering a child while being treated with Kyprolis. Consider the benefits and risks of Kyprolis and possible risks to the fetus when prescribing Kyprolis to a pregnant woman. If Kyprolis is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of Kyprolis in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Kyprolis and any potential adverse effects on the breastfed infant from Kyprolis or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Kyprolis can cause fetal harm. Advise female patients of reproductive potential to use effective contraceptive measures or abstain from sexual activity to prevent pregnancy during treatment with Kyprolis and for at least 30 days following completion of therapy. Advise male patients of reproductive potential to use effective contraceptive measures or abstain from sexual activity to prevent pregnancy during treatment with Kyprolis and for at least 90 days following completion of therapy.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of 598 patients in clinical studies of Kyprolis monotherapy dosed at 20/27 mg/m^2 by up to 10-minute infusion, 49% were 65 and over, while 16% were 75 and over. The incidence of serious adverse events was 44% in patients < 65 years of age, 55% in patients 65 to 74 years of age, and 56% in patients ≥ 75 years of age. In a single-arm, multicenter clinical trial of Kyprolis monotherapy dosed at 20/27 mg/m^2 (N = 266), no overall differences in effectiveness were observed between older and younger patients.

Of 392 patients treated with Kyprolis in combination with lenalidomide and dexamethasone, 47% were 65 and over and 11% were 75 years and over. The incidence of serious adverse events was 50% in patients < 65 years of age, 70% in patients 65 to 74 years of age, and 74% in patients ≥ 75 years of age. No overall differences in effectiveness were observed between older and younger patients.

Of 463 patients treated with Kyprolis dosed at 20/56 mg/m^2 by 30-minute infusion in combination with dexamethasone, 52% were 65 and over and 17% were 75 and over. The incidence of serious adverse events was 44% in patients < 65 years of age, 50% in patients 65 to 74 years of age, and 57% in patients ≥ 75 years of age. No overall differences in effectiveness were observed between older and younger patients.

8.6 Hepatic Impairment

Reduce the dose of Kyprolis by 25% in patients with mild or moderate hepatic impairment. Dosing recommendation cannot be made for patients with severe hepatic function.

The pharmacokinetics and safety of Kyprolis were evaluated in patients with advanced malignancies who had either normal hepatic function, or mild (bilirubin > 1 to 1.5×ULN or AST > ULN), moderate (bilirubin > 1.5 to 3×ULN), or severe (bilirubin > 3×ULN) hepatic impairment. The AUC of carfilzomib increased by approximately 50% in patients with mild and moderate hepatic impairment compared to patients with normal hepatic function. PK data were not collected in patients with severe hepatic impairment. The incidence of serious adverse events was higher in patients with mild, moderate, and severe hepatic impairment combined (22/35 or 63%) than in patients with normal hepatic function (3/11 or 27%).

Monitor liver enzymes regularly, regardless of baseline values, and modify dose based on toxicity.

8.7 Renal Impairment

No starting dose adjustment is required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic hemodialysis. The pharmacokinetics and safety of Kyprolis were evaluated in a Phase 2 trial in patients with normal renal function and those with mild, moderate, and severe renal impairment and patients on chronic hemodialysis. In addition, a pharmacokinetic study was conducted in patients with normal renal function and end-stage renal disease (ESRD).

In these studies, the pharmacokinetics of Kyprolis was not influenced by the degree of baseline renal impairment, including the patients on hemodialysis. Since dialysis clearance of Kyprolis concentrations has not been studied, the drug should be administered after the hemodialysis procedure.

The risk information provided here is not comprehensive. The FDA-approved product labeling can be found at www.kyprolis.com or contact Amgen Medical Information at 1-800-772-6436.

This Brief Summary is based on the Kyprolis Prescribing Information v15, 05/17.

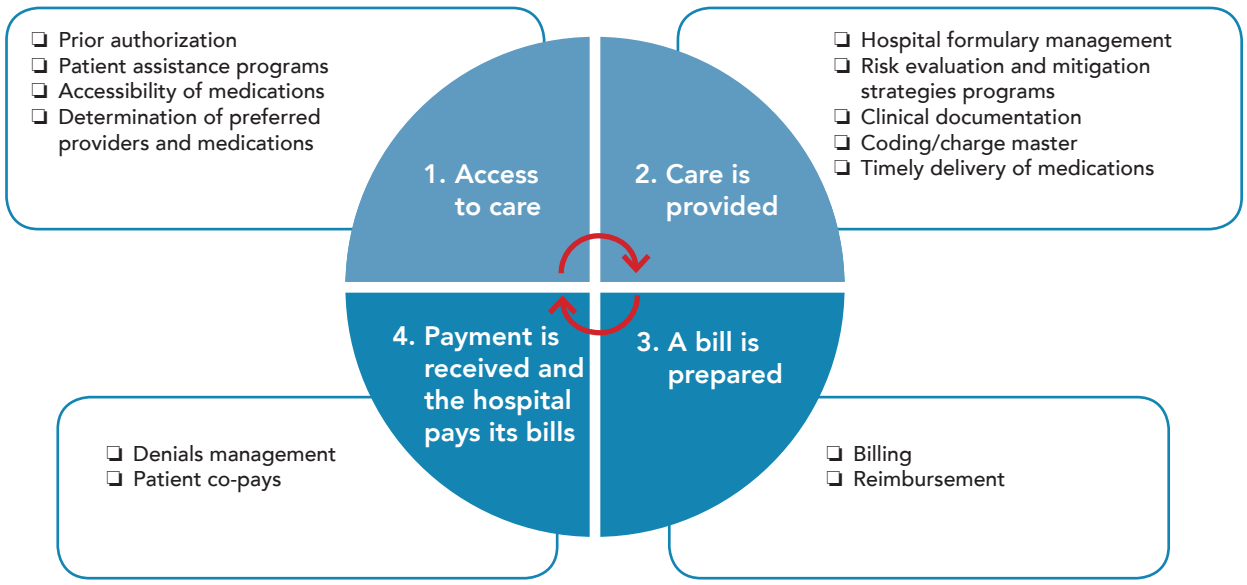
U.S. Patent Numbers: http://pat.amgen.com/kyprolis

www.ajmc.com/about/ebo
EBOncology

SPECIAL ISSUE/Pharmacists in Cancer Care
OCTOBER 2017
VOLUME 23, ISSUE 12

SP470

Pharmacy Team Engagement in Revenue Cycle Management



FEATURES

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Pharmacy Changes to Meet the Patient's Needs


MIKE HENNESSY, SR

MOST PATIENTS WHO PICK UP prescriptions give little thought to the process that goes into getting from the scribble on a doctor's pad to the white bag waiting for them at the counter. Today, there are a host of players involved and decisions to be made, and nowhere is the process more complex than in cancer care. Fortunately, as we learn in this issue of *Evidenced-Based Oncology*™ (*EBO*™), pharmacists in oncology care are rising to the occasion to meet both the changing needs of practices and to improve patient outcomes.

First, as Molly Billstein Leber, PharmD, BCPS, FASHP, writes, just getting a specialty drug on formulary is an adventure; once included, there is the decision about whether the drug will be a preferred agent, because the rise of pharmacy benefit managers, their pricing decisions, and rebates may conflict with hospital formulary decisions. As Leber writes, Pharmacy & Therapeutic (P&T) committees increasingly focus on cost and will need to change the way they do business—with more input from medical staff and information on the insurer and patient mix. Cost cannot be ignored, but P&T committees must do more to assess *value*.

With rising costs comes the recognition that more patients take oral medications. If patients take them at home away from the watchful eyes of medical staff, how can the practice know they are being taken correctly—or at all? Stacey McCullough, PharmD, and Ricky Newton, CPA, address this issue in their discussion of the transition from infused to oral therapies. Just as clinics create a remote space for patients to receive chemotherapy, it is necessary for pharmacy staff to have similar opportunities to thoroughly review oral oncolytics with patients, to ensure that patients and caregivers know how and when to take medications, what to expect in terms of side effects, what patients can eat, and what to do if a patient misses a dose.

The increased complexity of cancer therapy and the need for quality standards caused the National Community Oncology Dispensing Association, Inc (NCODA), to create education materials called Positive Quality Interventions, or PQIs. This platform is created with both the pharmacist and the patient in mind and is designed to help manage toxicities to keep patients on therapy, to efficiently manage dispensing processes, and to zero in on issues associated with oral cancer drugs. As Joshua Nubla, PharmD; Neal Dave, PharmD; and Michael Reff, RPh, MBA, discuss, NCODA members in both large and small practices contribute data to figure out whether PQIs helped patients stay on therapy longer or avoid trips to the emergency department, thus extending the conversation about quality.

Cancer care will only become more challenging, and as this issue of *EBO*™ demonstrates, fully recognizing the value of the pharmacist will benefit both patients and practices.

Thank you, as always, for following the developments in cancer care through *EBO*™. These discussions will come full circle at our annual meeting, Patient-Centered Oncology Care®, November 16-17, in Philadelphia. Register here if you haven't done so already: ajmc.com/meetings/pcoc17. ◆

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

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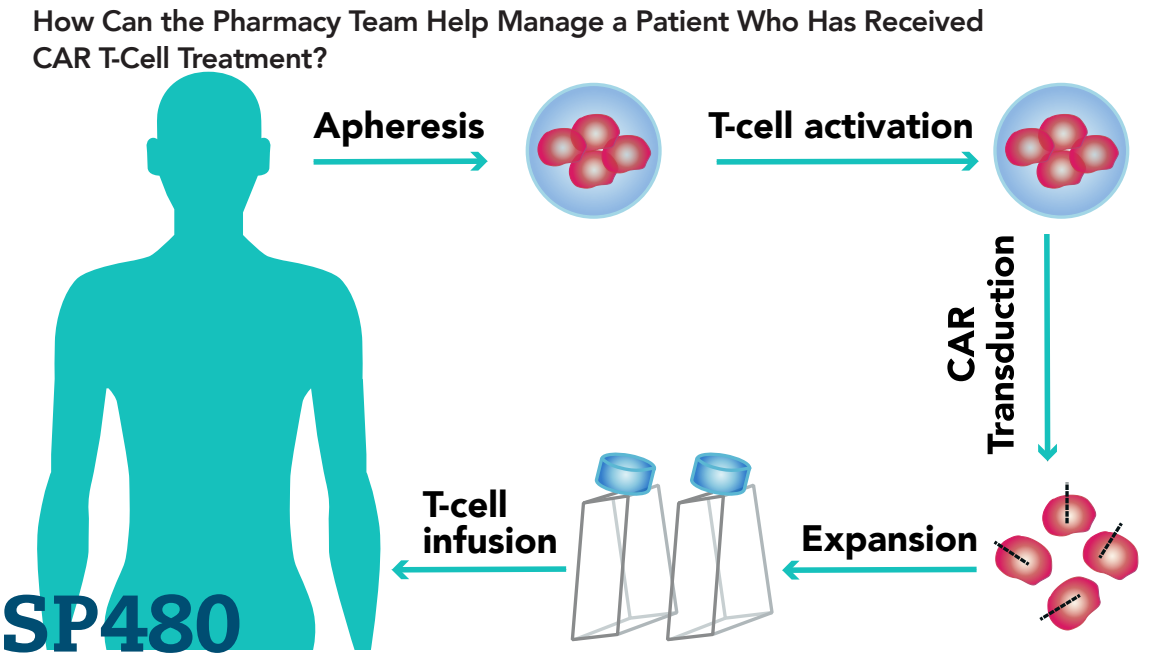
OCTOBER 2017, VOLUME 23, ISSUE 12



FROM THE EDITOR-IN-CHIEF

Oncology Pharmacist: An Important Team Player in Value-Based Care

THE FIELD OF CANCER CARE IS in the midst of unprecedented change. Part of this extraordinary revolution has been driven by a period of exceptional scientific innovation that has fundamentally changed the nature of cancer diagnosis and treatment. Accompanying significant increases in the cost of delivering these new technologies have challenged the economic sustainability of our cancer care delivery system and provoked changes in healthcare infrastructure and care reimbursement, including large-scale consolidations within the healthcare system such that physicians are now more likely to be employed by large medical groups or hospital-based healthcare systems than has been the historic norm. In addition, moves by government and third-party payers to place healthcare systems and providers at greater financial risk for the cost of cancer care delivery have led the evolution toward risk-bearing advanced alternative payment systems[1] and value-based payment models.[2] As cancer care has evolved from the use of clinic- or hospital-based chemotherapeutic regimens toward targeted therapeutics that are frequently dispensed as oral, outpatient agents, patients and their families are faced with an increasingly complex set of responsibilities and challenges.

As physicians, patients, families, and healthcare systems grapple with the complexity of delivering effective cancer care—sustainably, and in an increasingly patient-centered way—we have seen a shift away from care delivery by the solo oncologist toward care delivery by a highly integrated, diverse healthcare team. Within the context of this high-functioning cancer care delivery team, the pharmacist has assumed an increasingly complex and vital role in care delivery. In this issue of *Evidence-Based Oncology*™ (*EBO*™), we focus upon the evolving role of the onsite pharmacist in empowering more effective and efficient cancer care delivery.


JOSEPH ALVARNAS, MD

In their quest to move toward patient-centered care delivery models, pharmacies and pharmacists have a unique opportunity to provide more patient-facing services than in the prior era. Toward that end, onsite pharmacists can help patients and families navigate the challenges of compliance with increasingly complex therapeutic regimens, management of the unique complications of innovative therapeutics, and the potential financial toxicity related to therapeutic cost sharing. Pharmacists can also play a central role in adapting to value-based care delivery. In a recent review of the value-added benefits of including pharmacists in the onsite care delivery team, the authors noted that:

Pharmacists work with the oncology team to deliver a wide variety of services to patients, including education, aiding with chemotherapy order writing, monitoring [adverse effects], evaluating drug–drug and drug–disease interactions, and providing supportive care. Supportive care services may include those for nausea and vomiting, pain management, constipation and diarrhea, anemia, anticoagulation, and treatment with anti-infectives.[3]

Beyond their supportive care role toward patients and their families, pharmacists can contribute to building more robust and sustainable care delivery models by influencing the development and deployment of care pathways, their oversight role in value-based utilization management, formulary management, and more effective linkage of outcomes data in care planning.

In this issue of *EBO*™, Molly Billstein Leber, PharmD, BCPS, FASHP, Yale New Haven Health System, describes the importance of formulary management for a large healthcare system. Ray Bailey, FCS, and Ricky Newton, CPA, from Community Oncology Pharmacy Association, describe the realities of pharmacy benefits managers in the delivery of oncology care. In a separate piece, Newton, with co-author Stacey McCullough, PharmD, from Tennessee Oncology, reviews the changing role of the pharmacist in facilitating care transitions from infused to oral therapeutics. Finally, Brandon Shank, PharmD, MPH, BCOP; Phuoc Anh Nguyen, PharmD, MS, BCPS; and Emily Pherson, PharmD, BCPS, discuss the importance of pharmacy involvement in helping navigate the revenue cycle for high-cost medications.

Given the profound shifts in the oncology care model, the ability to leverage the extraordinary skills and capacities of the pharmacist will be essential for physicians and healthcare systems to make the leap toward value-based care delivery. The increasing burden that is placed upon patients, families, and healthcare systems as we enter a new era of targeted therapeutics; the increasingly complex payer environment; the increased patient-borne costs of care; and the need for greater stewardship over an increasingly complex and expensive therapeutic armamentarium require that the healthcare team evolve to more effectively meet these needs. An effective systems-based pharmacist can be an essential leader in this evolution. ◆

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Pharmacy's Changing Role as Cancer Care Transitions From Infused to Oral Therapies

Stacey McCullough, PharmD, and Ricky Newton, CPA

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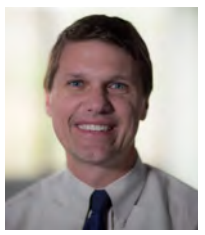
McCULLOUGH



NEWTON

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AN INCREASING NUMBER OF CANCER drugs are now delivered in oral formulations, with an estimated 25% to 35% in the research pipeline being orals. Increasingly, patients prefer to receive their oral cancer drugs and ancillary oral therapies in a safe, reliable, accessible, and affordable environment, tightly integrated with their overall cancer care. Depending on state pharmacy laws, community cancer clinics have established facilities to dispense oral drugs operating either under the physician's license or as in-practice closed-door pharmacies.

With the advent of oral oncolytics, a pharmacy's role has expanded far beyond compounding chemotherapy drugs for infusion. This evolution has created a beneficial physician extension for oral therapies in the care and management of patients treated in a home environment. Today's pharmacy teams are comprehensive, including patient access coordinators, financial counselors, and clinical staff to help navigate prescription benefits, secure co-pay assistance, educate patients on what can be complex dosing schedules, and provide specific information on potential side effects. Through strategically scheduled interactions, based on drug care plans, pharmacy staff routinely engage patients, assessing both adherence and tolerance to therapy.

Pharmacy Accreditation

As the role of pharmacies in providing care increases in prominence, so does the corresponding need to ensure quality standards and best practice benchmarks, both in general operations and patient outcomes. Pharmacy accreditation is an important way to achieve those needs.

Accreditation is an external and independent review that provides an imprimatur of a pharmacy's current policies, procedures, overall operations, and quality assurance programs. In seeking accreditation, pharmacies demonstrate their commitment to providing the highest quality service by complying with stringent national regulations and industry best practices. Common specialty pharmacy accreditations include:

- Accreditation Commission for Health Care (ACHC)
- Utilization Review Accreditation Commission

Most insurers require specialty pharmacy accreditation for application to their network, which is a means of demonstrating to the patient and payer that pharmacy services are on par with other pharmacy providers.

ACHC Accreditation

The Community Oncology Pharmacy Association (COPA) and ACHC have partnered to create educational resources and a customized suite of specialty pharmacy accreditation offerings.[1] In addition, standards for an oncology-specific accreditation have been jointly established by ACHC and COPA.[2] Undergoing both ACHC specialty pharmacy and oncology sub-specialty accreditation demonstrates proficiency in operations and patient-centric care plans specific to the complex care of oncology and hematology patients.

Patient Education

Oral oncolytics are powerful chemotherapeutic agents and have the same benefits and risk as intravenously administered drugs. With the convenience of patients taking the medication at home comes responsibilities for both the patient and the oncology practice. Patients must fully engage and commit to their care plan, including adherence to taking their medication(s) exactly as prescribed. Additionally, the oncology practice must create a remote "chemo suite" environment. Just as nursing and clinic staff establish relationships and dialogue with patients while receiving infused therapy, pharmacy staff have a similar opportunity and responsibility for patients receiving oral therapy. Because oral drugs are not taken under the direct, watchful eye of the physician, patient education and understanding of their medication is paramount to successful outcomes. Important areas for discussion include medication names (both trade and generic); how the medication works; when to begin taking the medication and how to take it, including details on days of the week and best time of day; how to take medication in relation to food and other medications; what to do if a dose is missed; and who to call if you have questions.

Patient education must also include an in-depth discussion of potential side effects and adverse reactions. Patients and/or caregivers must be taught to recognize symptoms as early as possible and be equipped with information to mitigate or manage side effects. Knowing how, when, and who to call to report the occurrence of any side effects and reactions helps minimize missed doses, discontinuation of therapy, or poor outcomes to therapy. This may require 24/7 on-call staff to address patient concerns or questions and access to both their complete pharmacy profile and electronic health record (EHR).

Patient Monitoring

The efficacy of many oral agents allows a pharmacy's relationship with patients to continue for several years. Monthly refill calls, especially when performed by the same pharmacy staff member, establish a rapport that allows a congenial exchange while ensuring medication adherence and tolerance.

Completing the Pharmacy Transition

Innovation in the development of new cancer treatments has significantly increased the number of oral treatment options and expanded opportunities for the pharmacy's role in patient care and management. Today's pharmacy team understands the various aspects of oral therapies, from benefits investigation to co-pay assistance and initial education to long-term adherence. Both, community oncology practices with in-house physician dispensing and licensed pharmacies can access complete patient charts within EHRs. Pharmacy staff working directly with the oncologist and their care extenders are poised to provide best management and better outcomes for patients receiving oral oncolytic treatments. For many patients on oral cancer drugs, pharmacy staff have become a regular contact and the most frequently accessible resource in their cancer care. ◆

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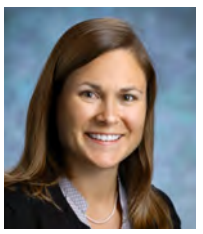
Pharmacy Team Engagement in Navigating the Revenue Cycle for High-Cost Medications in Patients With Cancer

Brandon R. Shank, PharmD, MPH, BCOP; Phuoc Anh (Anne) Nguyen, PharmD, MS, BCPS; and Emily C. Pherson, PharmD, BCPS

SHANK



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HEALTHCARE TEAMS FUNCTIONING IN today's evolving healthcare landscape shoulder the responsibility of delivering high-quality care while reducing costs throughout the entire revenue cycle. This cycle encompasses several key steps to appropriately bill patients and third party providers and capture revenue. The major components of the revenue cycle include patient access, clinical documentation, coding, billing processes, denial management, and reimbursement.[1] To optimize the revenue cycle, key stakeholders, including clinicians, financial staff, and institutional leadership, need to be engaged in the process to maximize reimbursement for the health system and minimize patient costs and burden. Pharmacists and pharmacy staff play a pivotal role in cost containment through optimization of medication regimens and engagement in the revenue cycle, particularly for high-cost medications (**Figure 1**).[1,2] The high-cost medications referred to in this article are those commonly used in the treatment of patients with cancer, such as oral antineoplastics, immunosuppressants, antifungals, and select anticoagulants.

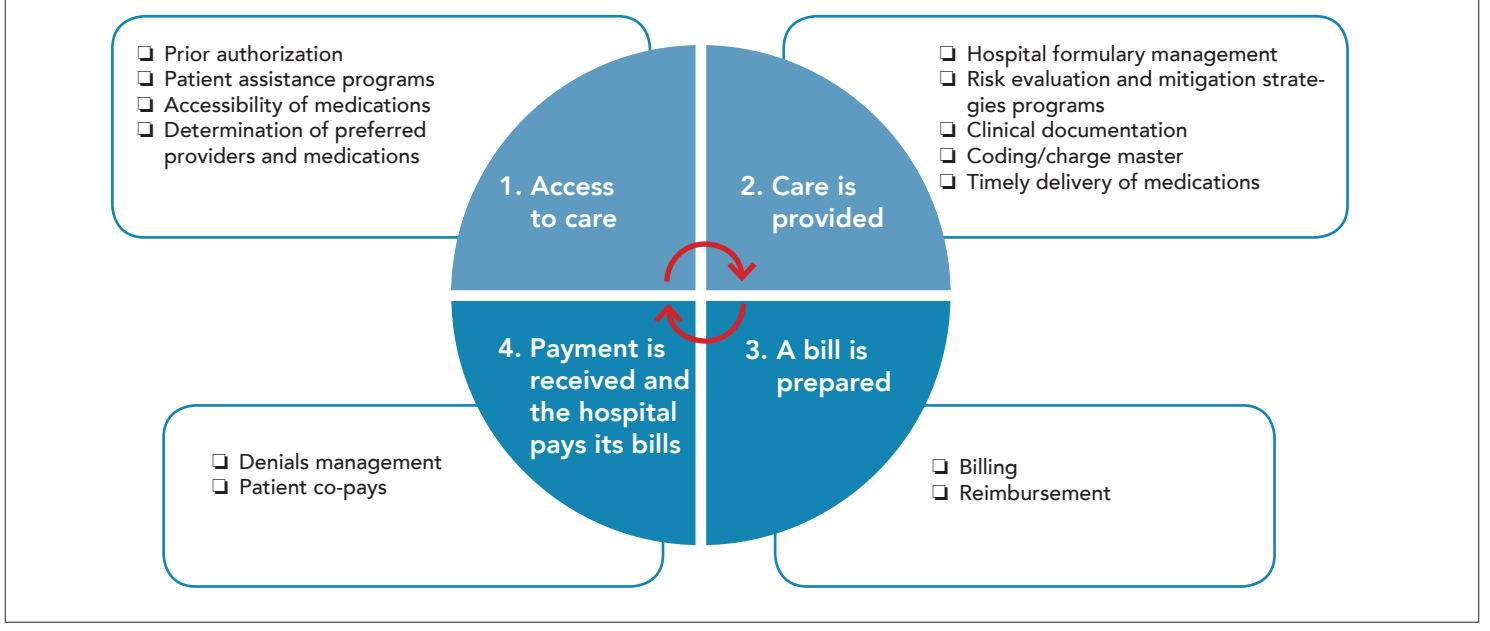
To facilitate the billing process, the medications must be appropriately coded. Every hospital has a charge description master, which includes the general ledger number, product description, billing units, Healthcare Common Procedure Coding Systems (HCPCS) codes, revenue codes, and pricing information.[3] With constant updates to CMS' billing requirements and rapid changes in the drug market of new brand and generic medications, there is a high possibility that HCPCS codes can easily become outdated or incorrectly associated with a medication. For example, blinatumomab (Blincyto), approved in 2014 for the treatment of Philadelphia chromosome–negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia, had different HCPCS codes for 2015 (J7799) and 2016 (J9039).[4] It is essential for hospital and pharmacy leadership to understand the financial implications of such changes. These leaders should include individuals well-versed in charge coding and actively engaged in the ever-changing drug market and insurance industry.

Growing Drug Costs

In addition to the complexities associated with billing, the problem of sky-rocketing drug prices has garnered much attention in recent years and made budget management more complex. In its annual report on national trends in prescription projections and spending, the American Society of Health-System Pharmacists (ASHP) showed a 6% increase in US prescription sales between 2015 and 2016, totaling $448.2 billion in 2016.[5] Overall, adalimumab was associated with the highest overall spend in 2016 with $13.6 billion in expenditures; in clinics and nonfederal facilities, infliximab had the highest expenditure with $5.3 billion in spending.[5]

Nonfederal facilities are defined as licensed hospitals that are not owned by the government, including inpatient treatment and rehabilitation facilities. Nonfederal facilities also include general and specialty acute care institutions. Federal facilities refer to US ships or hospitals that belong to the Public Health Service, the Veterans Health Administration, and other federal branches. Higher drug prices and more prescribing were primarily responsible for the growth in expenditure in nonfederal hospitals and clinics.[5] Drug expenditures in 2017 are projected to increase 6% to 8% overall and by 3% to 5% in hospitals.[5] Therefore, health-system pharmacy leaders and clinicians should be actively engaged in the revenue cycle process and develop strategies that emphasize cost containment and ensure optimal medication reimbursement.[2,6,7]

FIGURE 1. Steps of Pharmacy Team Engagement in Revenue Cycle Management[1,2]



Top 5 Opportunities for Pharmacy Team Engagement in Containing Drug Costs and Maximizing Reimbursement in Patients Undergoing Cancer Treatment

Pharmacists caring for patients undergoing cancer treatment are in a unique position to help other providers and patients navigate the convoluted reimbursement structure. Strategies include finding suitable therapeutic alternatives to meet the needs of formulary restrictions or obtaining approval for off-label use of agents. Starting upon admission and continuing post discharge, transitions-of-care pharmacy team members provide continuity of care and enhance medication adherence. Transitions-of-care pharmacy team efforts, starting upon admission and continuing through discharge, can ensure coverage and enhance medication adherence.

When it may not be appropriate to transition a patient to a hospital formulary medication, the hospital may elect to order the medication and dispense it from their inventory.

Many antineoplastic and supportive care medications are expensive and/or challenging to obtain. Timely acquisition is essential in order to initiate cancer treatment expeditiously. This article reviews key strategies that pharmacy team members can utilize to optimize medication-related revenue cycle compliance, including prior authorizations (PAs), hospital formulary management, patient assistance programs, accessibility of medications, and risk evaluation and mitigation strategies (REMS) programs.

1. Managing inpatients who are taking medications outside of the hospital formulary as outpatients.

Hospital formularies ensure safe, efficacious, and cost-effective medication use in the inpatient setting, especially for high-cost medications.[6] Medications included on a hospital formulary vary based on an institution's patient population and contracting options, among other factors. Strategies to appropriately manage admitted patients who continue to take medications as outpatients that are not included on the inpatient hospital formulary include therapeutic interchanges, nonformulary review processes, and using the patients' own medication(s) during their hospital stay.

A therapeutic interchange is a tool that provides a roadmap to transition patients from an outpatient medication that is not on the hospital formulary to a medication that is included, and this often presents healthcare providers with a medication that has an equivalent dosage as the formulary medication.[8] For example, if a patient was taking candesartan 8 mg by mouth once daily as an outpatient and losartan was the hospital formulary angiotensin receptor blocker, a therapeutic interchange would direct prescribers to order losartan 50 mg orally once daily. These interchanges are most effective when the electronic health record (EHR) automatically directs prescribers to this alternate choice when the nonformulary drug is ordered. This strategy alerts prescribers that they are attempting to order a nonformulary medication and presents them instantly with alternatives. Some institutions utilize automatic therapeutic interchanges whereby the pharmacist, upon order verification, would automatically make the switch to the appropriate formulary medication. Developing therapeutic interchanges requires appropriate research and evidence supporting the specific interchange so that the healthcare team has information readily available.

For a medication that is not a part of an institution-approved therapeutic interchange, most institutions have a process in place whereby pharmacists are responsible for reviewing nonformulary medications and providing formulary alternatives, when appropriate.[9] Depending on the specific institutional practice, this may be built into the role of the pharmacist who is verifying orders or a pharmacist with specialized training in the particular therapeutic area may be consulted for reviewing and approving nonformulary medication use, if needed. By having a review process in place, prescribers can become accustomed to discussions with the pharmacist when ordering nonformulary medications to assist with providing formulary alternatives.

When it may not be appropriate to transition a patient to a hospital formulary medication, the hospital may elect to order the medication and dispense it from their inventory. In certain circumstances, if a patient brought the medication with them to the hospital, that may be used during the hospital stay. This may occur if waiting for the hospital to acquire the nonformulary medication poses a safety risk to the patient or if the medication requires a patient-specific distribution channel, such as a REMs program or clinical trial. Ensuring safe use of a medication brought in by a patient requires appropriate practices for ordering and verifying these medications. Many EHRs have an option to allow the prescriber to indicate that a patient's own medication may be used. This acts as a trigger for the verifying pharmacist to check the product by confirming identity and appropriate dating. When applicable, appropriate barcoding of the patient's own medication also needs to be accounted for using institution-specific practices.

An example of this in oncology practice is the tyrosine kinase inhibitor, dasatinib. If a hospital did not have this medication on formulary, it would not be clinically appropriate to substitute another agent during the hospital stay. If the patient brought his or her own supply to the hospital, it would be important to not interrupt therapy, to continue the medication using the patient's supply. Many hospital formularies do not include all oral antineoplastic agents; this becomes an important education point when prescribing oral chemotherapy in the outpatient setting by informing patients that they should be prepared to bring their own supply in the event of hospitalization.

Using a combination of the above strategies will prepare institutions to appropriately manage patients that are taking medications outside of the hospital formulary as they transition to being inpatient.

2. Setting patients up for success by facilitating coverage via outpatient prescription insurance.

Outpatient prescription insurance plans also have a formulary to optimize medication use for their members. Often, medications and criteria for their use differ between the hospital formulary and the outpatient insurance formulary. Additionally, preferred drugs may differ from institutional pharmacies based on contracting or rebates received from a pharmacy benefit manager (PBM). In order to best assist patients in navigating the outpatient prescription formulary, it is first necessary to access and interpret the outpatient formulary and then meet any requirements necessary to access the formulary medication.

One method to determine outpatient prescription coverage is to process a test claim through an outpatient pharmacy. This practice will adjudicate the prescription to make a coverage determination but then immediately cancel the claim to prevent the prescription from processing completely. To use this method, it is important to clarify the intention of the test claim to the outpatient pharmacy—safety and insurance issues can arise if prescribers are attempting to fill the same prescription multiple times. If one does not have access to a test claim process, some outpatient insurance plans will post their formulary information online. It is important to note that updates to these documents are determined by the individual insurance plans and may not correlate in real-time with decision changes.

For the most accurate information, it is best to contact the company via phone. Also, what is listed on the online formulary will not be specific to the patient in terms of any deductible or other patient-specific plan information, so contacting the insurance company directly or having the patient use their online portal to obtain the most accurate patient-specific information about coverage may be necessary. Several test claims of different drugs in a therapeutic class may be needed to help determine the preferred drug with the most affordable cost. It is important to remember that the test claim result is only an estimate specific to that pharmacy as the copay may differ at another pharmacy due to various insurance and pharmacy acquisition cost factors.

Once outpatient insurance coverage has been determined, it may be necessary to facilitate PA of the medication. The PA process typically requires the prescriber to review the patient's medical history and ensure that they meet certain criteria for medication use. PA approval can take place over the phone, even online in some instances, and an immediate determination could be made. Other cases require forms to be submitted via fax or online, and coverage determination may take 24 to 72 hours. Once issued, it is important to note that the standard timeframe for the PA is 1 year, but that it may be a shorter period »

in other instances and re-authorization must be obtained to ensure continuity of care.

An area of growing complexity, especially when navigating from the inpatient to the outpatient setting, is the realm of biosimilar medications. Although a hospital formulary may include one brand of a biologic, the outpatient PBM formulary may prefer another. An example of this is filgrastim, where a hospital formulary may include filgrastim-sndz (Zarxio), while the outpatient plan prefers filgrastim (Neupogen). This is also common with the new follow-on biologic for insulin glargine, Basaglar, which is becoming more common for outpatient formularies even though many hospitals still have Lantus or another basal insulin as their preferred product. Being aware of these different formulary preferences can help patients safely transition from inpatient to outpatient, avoiding interruptions in treatment or duplications in these high-risk medications.

3. Assisting patients to obtain drugs with no coverage or high co-pays

Patient assistance programs, private grants, and medication replacement programs are a few mechanisms that support patient access to medications.[10] Pharmaceutical manufacturers can provide assistance to obtain insurance approval and help patients get coverage for their medications. The provision of this assistance is often outsourced to a third-party company that oversees the disbursement of funds and/or free medications.

Most insurance plans have strict guidelines outlining which medications are covered within their plan. There are specific clinical scenarios with limited treatment options where a medication may need to be used off label or its FDA approval may be pending. In these situations, obtaining reimbursement from the insurance company can be challenging. Free distribution programs offered by pharmaceutical manufacturers provide an alternative to procuring expensive medications. However, the approval process can take several days to weeks, so starting early can prevent delays in treatment initiation. Submission of specific income documentation and copies of insurance denial is often required, which can be time-consuming to collect.

On an institutional level, many pharmacy departments have hired reimbursement coordinators/specialists, who may be pharmacy technicians or nonhealthcare individuals with a background in finance or health insurance. These individuals focus on PAs, drug replacement, co-pay assistance, and denial management and they work closely with the PBM and insurance companies to find alternatives and investigate co-pays for high-cost medications. They serve as a liaison to the financial offices at the hospital and coordinate with replacement drug programs to recover medications. Upon obtaining the power of attorney from patients, reimbursement coordinators can request co-pay assistance from manufacturers on the patients' behalf and provide valuable assistance, especially for patients who may be too ill or overwhelmed by the reimbursement process. The addition of pharmacy reimbursement coordinators/specialists has significantly reduced the amount of time pharmacists and other healthcare providers spend on getting drugs reimbursed for patients.[2] These programs often lead to increased outpatient prescription capture rates for institutional pharmacies. One institution increased its outpatient pharmacy's capture rate from 57% to 73% for the general pediatric service.[11]

For a medication that is not a part of an institution-approved therapeutic interchange, most institutions have a process in place whereby pharmacists are responsible for reviewing nonformulary medications and providing formulary alternatives, when appropriate.

There are exclusions for some programs, such as federal or state Medicare and Medicaid programs, where patients may not be allowed to receive co-pay assistance. This can be particularly difficult for patients who cannot afford high co-pays or for those who must first meet their deductible. Additionally, several private programs offer grants to cover out-of-pocket costs for patients undergoing cancer treatment. Being on funding cycles and considering their high demand, these grant programs are at risk of quickly exhausting their capital. It is important to have a backup plan in place and understand the extent of assistance that a patient may require so an entire treatment is covered.

4. Navigating patient registration for drugs requiring REMS programs

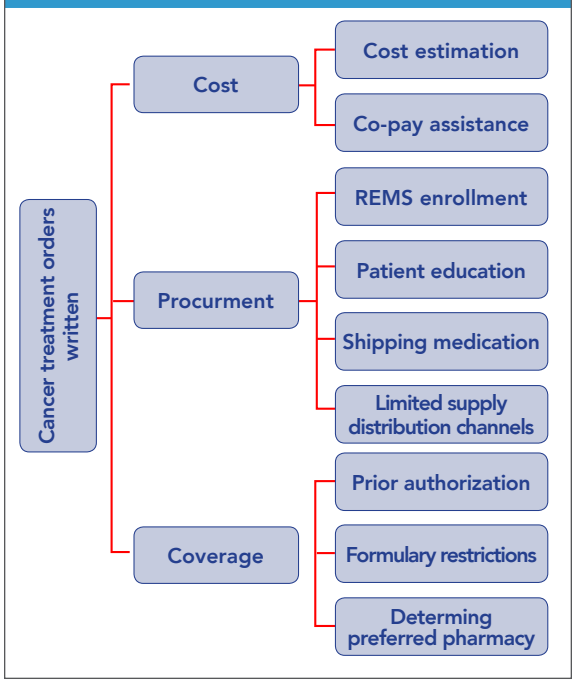
The FDA Amendments Act of 2007 gave the regulatory body authority to require a REMS from manufacturers to ensure that the benefits of a medication outweigh its risks (**Table**).[12,15] The drugs selected for REMS programs have been found to have safety risks, such as teratogenic effects; special initiation requirements; or communication mandates to the patient beyond a black box warning.[13] These programs often require the physician to undergo additional training to gain the privileges to prescribe these drugs. Patients also have to complete a survey, undergo education, and sometimes obtain the medication through a designated pharmacy. Medications such as thalidomide, lenalidomide, and pomalidomide, which can cause severe birth defects, require female patients to undergo pregnancy testing and all patients to agree to contraceptive use. While these added steps improve safety, the process significantly slows down drug procurement and complicates their use in the inpatient setting.[14]

In scenarios where the medication is distributed directly to the patient, patients must use their own supply during hospitalization. Outpatient pharmacies are required to adapt to the increasingly complex monitoring requirements of specialty medications that have limited distribution and high costs, require close monitoring or specialty handling, need patient

TABLE. Current Oncologic and Supportive Care Agents Requiring REMS[15]

Medication	Use
Alemtuzumab	B-cell chronic lymphocytic leukemia
Blinatumomab	B-cell precursor acute lymphoblastic leukemia
Idelalisib	Chronic lymphocytic leukemia Follicular B-cell non-Hodgkin lymphoma Small lymphocytic lymphoma
Ipilimumab	Melanoma
Lenalidomide	Multiple myeloma Mantle cell lymphoma Myelodysplastic syndromes
Panobinostat	Multiple myeloma
Pomalidomide	Multiple myeloma
Ponatinib	Chronic myeloid leukemia Philadelphia chromosome–positive acute lymphoblastic leukemia
Thalidomide	Multiple myeloma Erythema nodosum leprosum
Vandetanib	Medullary thyroid cancer
Supportive care	
Denosumab	Increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer Increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer
Eculizumab	Atypical hemolytic uremic syndrome Paroxysmal nocturnal hemoglobinuria
Romiplostim	Chronic immune thrombocytopenia

FIGURE 2. Challenges Associated With Procuring High-Cost Medications



REMS indicates Risk Evaluation and Mitigation Strategy.

or provider education, and are used in a unique patient population. This has resulted in a shift to higher utilization of specialty pharmacies, which are equipped to distribute specialty medications as they maintain adequate training and necessary procedures. PBMs often have preferred pharmacies, and it is time consuming to determine what the preferred pharmacy is for each patient.

There have been instances where a patient's insurance required a specific specialty pharmacy, but that pharmacy was unable to obtain a supply of the drug. These circumstances take a significant amount of time to manage and ensure patient access to the medication.

5. Timely delivery of medications

In certain circumstances, it may be urgent to start cancer treatment. However, we often experience delays with obtaining high-cost novel targeted medications. PAs delay drug procurement in addition to identifying the patient's preferred pharmacy, which is more often a mail order pharmacy (**Figure 2**) so that these medications need to be directly shipped to the patient. Providers and support staff spend a large amount of time on the phone with insurance representatives to obtain PA and ensure timely drug delivery, and specialty pharmacies work to ensure prompt delivery of medications as soon as approval is obtained. It is important to communicate with the pharmacy when urgent delivery is needed so the drug can be overnighted to the patient, if necessary.

Due to drug shortages or restricted use, some medications undergo limited supply distribution. For example, procarbazine, a drug used in combination treatment for lymphoma in the brain, is not carried by all pharmacies. There also have been instances where a patient's insurance required a specific specialty pharmacy, but that pharmacy was unable to obtain a supply of the drug. These circumstances take a significant amount of time to manage and ensure patient access to the medication.

It can be logistically challenging, especially for patients from out of town, to have their drugs delivered to a hotel or temporary residence. They often need someone to sign for the package, which requires the caregiver to leave the patient's bedside to obtain medications. Some medications require special handling, such as refrigeration, which adds complexity. Mail order prescriptions may have lower co-pays for chronic medications. If caregivers know medications will be delayed, they can defer the start of cancer treatment until the entire regimen can start at the same time—unless the patient's clinical situation prevents this. It is often difficult to predict what other medication needs may arise during a course of chemotherapy; therefore, a local community pharmacy is often necessary for obtaining medications to manage symptoms in a timely fashion. In addition, patients often have to rely on caregivers, friends, and relatives to ensure timely delivery of their medications, which may include personally carrying or mailing the medications to the patient's temporary location.

Conclusion

With the clinical and financial implications of high-cost medications, and their impact on health system revenue, it is of utmost importance for all key stakeholders to be engaged in the complex revenue cycle. Tackling PBMs' insurance formularies and the reimbursement process can be dynamic and complex. It is crucial for the pharmacy team to collaborate with other providers, hospital financial team members, PBMs, and hospital leadership and leverage their skill sets to manage costs and optimize reimbursement for the health system. Overall, this collaboration will maximize benefits for both institutions and patients, ultimately ensuring the most optimal use of medications. ◆

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#1 PRESCRIBED THERAPY ACROSS ALL LINES OF CLL SINCE NOVEMBER 2016.*
MORE THAN 25,000 PATIENTS TREATED SINCE APPROVAL[1†]

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

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

CLL
SLL

IMBRUVICA® (ibrutinib) is a kinase inhibitor indicated for the treatment of patients with:

- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)[2]
- CLL/SLL with 17p deletion[2]

*Based on market share data from IMS as of January 2017.
†Based on IMS data February 2014 to date.

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 up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half 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 postsurgery depending upon the type of surgery and the risk of bleeding.

Infections - Fatal and nonfatal infections have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Evaluate patients for fever and infections and treat appropriately.

Cytopenias - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13% to 29%), thrombocytopenia (range, 5% to 17%), and anemia (range, 0% to 13%) based on laboratory measurements occurred in patients treated with single agent IMBRUVICA®. Monitor complete blood counts monthly.

Atrial Fibrillation - Atrial fibrillation and atrial flutter (range, 6% to 9%) have occurred in patients treated with IMBRUVICA®, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new-onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension - Hypertension (range, 6% to 17%) has occurred in patients treated with IMBRUVICA® with a median time to onset of 4.6 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 antihypertensive medications and/or initiate antihypertensive treatment as appropriate.

Second Primary Malignancies - Other malignancies (range, 3% to 16%) including non-skin carcinomas (range, 1% to 4%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2% to 13%).

Tumor Lysis Syndrome - Tumor lysis syndrome has been infrequently reported with IMBRUVICA® therapy. Assess the baseline risk (eg, 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. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of

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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 not included in the RESONATE™-2 trial[3]

EXTENDED OVERALL SURVIVAL

IMBRUVICA® significantly extended OS vs chlorambucil[2]

Statistically significant reduction in risk of death[2]

56%

HR=0.44
(95% CI: 0.21, 0.92)

41% of patients crossed over to IMBRUVICA®

Estimated survival rates at 24 months

95% IMBRUVICA®
(95% CI: 89, 97)

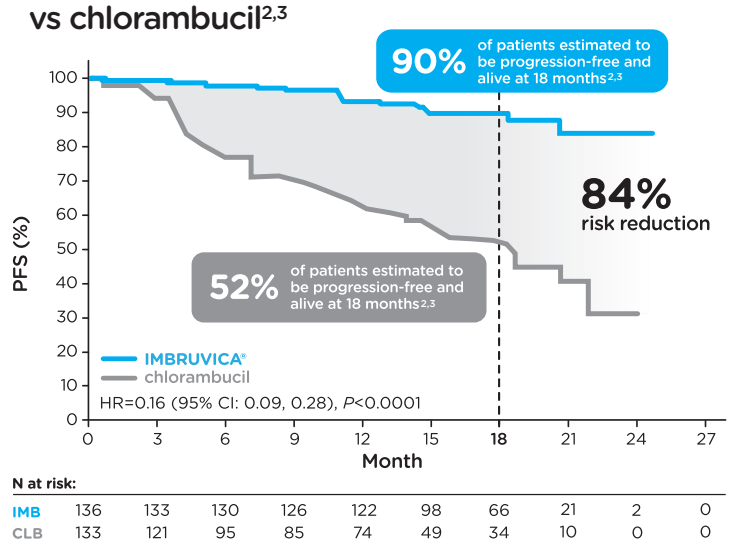
84% chlorambucil
(95% CI: 77, 90)

SECONDARY ENDPOINT: OS

- Median follow-up was 28 months[2]

PROLONGED PROGRESSION-FREE SURVIVAL

IMBRUVICA® significantly extended PFS vs chlorambucil[2,3]



PRIMARY ENDPOINT: PFS

- Median follow-up was 18 months[3]
- IMBRUVICA® median PFS not reached[2]
- Chlorambucil median PFS was 18.9 months (95% CI: 14.1, 22.0)[2]
- PFS was assessed by an IRC per revised iwCLL criteria[3]

Adverse reactions ≥20% across CLL/SLL registration studies[2]

- Neutropenia
- Thrombocytopenia
- Anemia
- Diarrhea
- Musculoskeletal pain
- Nausea
- Rash
- Bruising
- Fatigue
- Pyrexia
- Hemorrhage

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 commonly occurring adverse reactions in the phase 1b/2 and phase 3 trials in patients with CLL/SLL receiving IMBRUVICA® (≥ 20%) were neutropenia (40%)*, thrombocytopenia (23%)*, anemia (21%)*, diarrhea (42%), musculoskeletal pain (31%), nausea (30%), rash (30%), bruising (29%), fatigue (26%), pyrexia (23%) and hemorrhage (20%).

*Based on adverse reactions and/or laboratory measurements (noted as platelets, neutrophils, or hemoglobin decreased).

Approximately 4%-10% of patients discontinued treatment due to adverse reactions. Most common adverse reactions leading to discontinuation were pneumonia, hemorrhage, atrial fibrillation, rash, and neutropenia (1% each).

Approximately 6% of patients had a dose reduction due to adverse reactions.

DRUG INTERACTIONS

CYP3A Inhibitors - Avoid coadministration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA® dose.

CYP3A Inducers - Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment - Avoid use in patients with moderate or severe baseline hepatic impairment. In patients with mild 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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imbruvica®
(ibrutinib) 140mg capsules

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

Mantle Cell Lymphoma: IMBRUVICA is indicated for the treatment of 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 patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) *[see Clinical Studies (14.2) in Full Prescribing Information].*

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion *[see Clinical Studies (14.2) in Full Prescribing Information].*

Waldenström's Macroglobulinemia: IMBRUVICA is indicated for the treatment of patients with Waldenström's macroglobulinemia (WM) *[see Clinical Studies (14.3) in Full Prescribing Information].*

Marginal Zone Lymphoma: IMBRUVICA is indicated for the treatment of 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.

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 up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half 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 have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 29% of patients *[see Adverse Reactions].* Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 13%) based on laboratory measurements occurred in patients treated with single agent IMBRUVICA.

Monitor complete blood counts monthly.

Atrial Fibrillation: Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. Atrial fibrillation should be managed 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 (range, 6 to 17%) has occurred in patients treated with IMBRUVICA with a median time to onset of 4.6 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 (range, 3 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2 to 13%).

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 embryofetal 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]*
- Atrial Fibrillation *[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 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* Decrease of Hemoglobin, Platelets, or Neutrophils 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 and three randomized controlled clinical trials in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1 included 51 patients with previously treated CLL/SLL, Study 2 included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, Study 3 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil and Study 4 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 1, 2, 3 and 4 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 1, 2, 3 and 4 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 1: 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 1

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

The most commonly occurring adverse reactions in Studies 5 and 6 (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, fatigue, bruising, hemorrhage, anemia, rash, musculoskeletal pain, and nausea.

Nine percent of patients receiving IMBRUVICA across Studies 5 and 6 discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 10% of patients.

Study 5: 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 5.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 5 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
Infections and infestations	Upper respiratory tract infection	19	0
	Sinusitis	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

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

Table 10: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with WM in Study 5 (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	43	13
Neutrophils Decreased	44	19
Hemoglobin Decreased	13	8

* Based on laboratory measurements.

Study 6: Adverse reactions and laboratory abnormalities described below in Tables 11 and 12 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 6.

Table 11: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 6 (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.

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Table 12: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MZL in Study 6 (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

* Based on laboratory measurements.

Additional Important Adverse Reactions: *Diarrhea:* Diarrhea of any grade occurred at a rate of 43% (range, 36% to 59%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 14%) and Grade 3 in 3% (range, 0 to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 10 days (range, 0 to 627), of Grade 2 was 39 days (range, 1 to 719) and of Grade 3 was 74 days (range, 3 to 627). Of the patients who reported diarrhea, 82% had complete resolution, 1% had partial improvement and 17% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 85 days (range, 1 to 414 days). Of the patients with visual disturbance, 61% had complete resolution and 38% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 335 days).

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

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

DRUG INTERACTIONS

CYP3A Inhibitors: Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A (CYP3A). In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng • hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid concomitant administration of IMBRUVICA with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting IMBRUVICA therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of IMBRUVICA toxicity *[see Dosage and Administration (2.4) in Full Prescribing Information].*

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A *[see Dosage and Administration (2.4), and Clinical Pharmacology (12.3) in Full Prescribing Information].*

CYP3A Inducers: Administration of IMBRUVICA with rifampin, a strong CYP3A inducer, decreased ibrutinib C_{max} and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction *[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. 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 malformations *[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.

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.

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 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.

The most commonly occurring adverse reactions in Studies 5 and 6 (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, fatigue, bruising, hemorrhage, anemia, rash, musculoskeletal pain, and nausea.

Nine percent of patients receiving IMBRUVICA across Studies 5 and 6 discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 10% of patients.

Study 5: 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 5.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 5 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
Infections and infestations	Upper respiratory tract infection	19	0
	Sinusitis	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

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

Table 10: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with WM in Study 5 (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	43	13
Neutrophils Decreased	44	19
Hemoglobin Decreased	13	8

* Based on laboratory measurements.

Study 6: Adverse reactions and laboratory abnormalities described below in Tables 11 and 12 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 6.

Table 11: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 6 (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.

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Table 12: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MZL in Study 6 (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

* Based on laboratory measurements.

Additional Important Adverse Reactions: *Diarrhea:* Diarrhea of any grade occurred at a rate of 43% (range, 36% to 59%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 14%) and Grade 3 in 3% (range, 0 to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 10 days (range, 0 to 627), of Grade 2 was 39 days (range, 1 to 719) and of Grade 3 was 74 days (range, 3 to 627). Of the patients who reported diarrhea, 82% had complete resolution, 1% had partial improvement and 17% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 85 days (range, 1 to 414 days). Of the patients with visual disturbance, 61% had complete resolution and 38% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 335 days).

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

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

DRUG INTERACTIONS

CYP3A Inhibitors: Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A (CYP3A). In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng • hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid concomitant administration of IMBRUVICA with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting IMBRUVICA therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of IMBRUVICA toxicity *[see Dosage and Administration (2.4) in Full Prescribing Information].*

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A *[see Dosage and Administration (2.4), and Clinical Pharmacology (12.3) in Full Prescribing Information].*

CYP3A Inducers: Administration of IMBRUVICA with rifampin, a strong CYP3A inducer, decreased ibrutinib C_{max} and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction *[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. 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 malformations *[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.

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.

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 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.

IMBRUVICA® (ibrutinib) capsules

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

Geriatric Use: Of the 905 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 21% 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: Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function.

The safety of IMBRUVICA has not been evaluated in cancer patients with mild to severe hepatic impairment by Child-Pugh criteria.

Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with moderate or severe hepatic impairment (Child-Pugh class B and C) *[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].*
- *Atrial fibrillation:* 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 capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day *[see Dosage and Administration (2.1) in Full Prescribing Information].*
- 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 capsules to make up the missed dose *[see Dosage and Administration (2.6) in Full Prescribing Information].*
- 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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and
Marketed by:
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PRC-02460

In Conversation With a Pharmacist: Management of CAR T-Cell Treatment

Surabhi Dangi-Garimella, PhD

SHANK

Brandon R. Shank, PharmD, MPH, BCOP, is a clinical pharmacy specialist, The University of Texas MD Anderson Cancer Center.

IN AUGUST 2017, the drug manufacturer Novartis became the first company to receive a green light from the FDA to market its chimeric antigen receptor T (CAR T)-cell gene therapy treatment. Tisagenlecleucel (Kymriah) has been approved for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL) in a pediatric population (**see sidebar**).

Speaking with *Evidence-Based Oncology*™ (*EBO*™), Brandon R. Shank, PharmD, MPH, BCOP, clinical pharmacy specialist, Division of Pharmacy, The University of Texas MD Anderson Cancer Center, shared his experience with this treatment in his clinic. He explained the changes he anticipates may be needed for a safe, effective adoption of this new treatment modality in the oncology clinic.

***EBO*™: Can you start by giving us a clinical understanding of the CAR T-cell therapy?**

SHANK: CAR T-cell therapy is a specific kind of therapy for patients in which T cells are trained to attack a specific antigen. One specific group so far is in ALL [acute lymphoblastic leukemia], and the specific product developed has an anti-CD19 on it. So, the patients undergo leukapheresis and then they are infused with cells that have been trained to attack the cancer, specifically leukemia—either acute or chronic. There are trials currently underway [that are testing] these cells in lymphoma and also in multiple myeloma with a different target. There are also trials evaluating different antigens on these CAR T cells.

This treatment has revolutionized cancer [care] because we have moved away from standard chemotherapy—although there is a place of CAR T cells getting a conditioning regimen with fludarabine or cyclophosphamide. [Overall, though,] we are moving away from the actual chemotherapy and instead, training the body's immune system to fight the cancer.

***EBO*™: What specific role do you play in delivering CAR T-cell infusion to patients?**

SHANK: My role is in the inpatient lymphoma service, specifically, with managing the logistics of the pharmacotherapy and toxicities of CAR T cells.

On the formulary management side, hospitals now have to deal with adding 2 expensive medications—anti–IL-6 [interleukin-6] medications called siltuximab and tocilizumab—which are used to manage CRS [cytokine release syndrome]. So, from a formulary standpoint, institutions will need to develop order sets and make appropriate restrictions for the use of these agents.

Currently, most of my role on the service is to provide the supportive care and to manage the CRS and the CRES [CAR T-cell–related encephalopathy syndrome]. The pathophysiology of CRES overlaps with CRS, but this is specifically divided out to having encephalopathy. It's a related but separate toxicity that's been described recently by Neelapu, et al.

***EBO*™: Can you describe the coordination among the various care providers when managing the toxicities associated with CAR T-cell infusion?**

SHANK: An interdisciplinary team [includes] the oncologist, the attending physician, the nurse practitioner, emergency [department] physicians, neurologists, ICU [intensive care unit] physicians, and other specialties. Many consult services, such as the neurology team, will assess the patients daily. As soon as I hear of an adverse effect, most commonly fever, we [begin] our sepsis work-up, starting intravenous antibiotics, and all this has to be done in a rapid manner as CRS can be a rapidly progressing syndrome.

We ensure that we avoid medications that would overlap or have overlapping toxicities, such as central nervous system suppressants, which could affect the differential assessment of the patients who develop CRS. We also avoid contraindicated medications, such as steroids. We have to monitor patients' blood pressure, fluids, and electrolyte status, and also ensure that their home medications are continued or held if appropriate, as well as to start our standard prophylaxis.

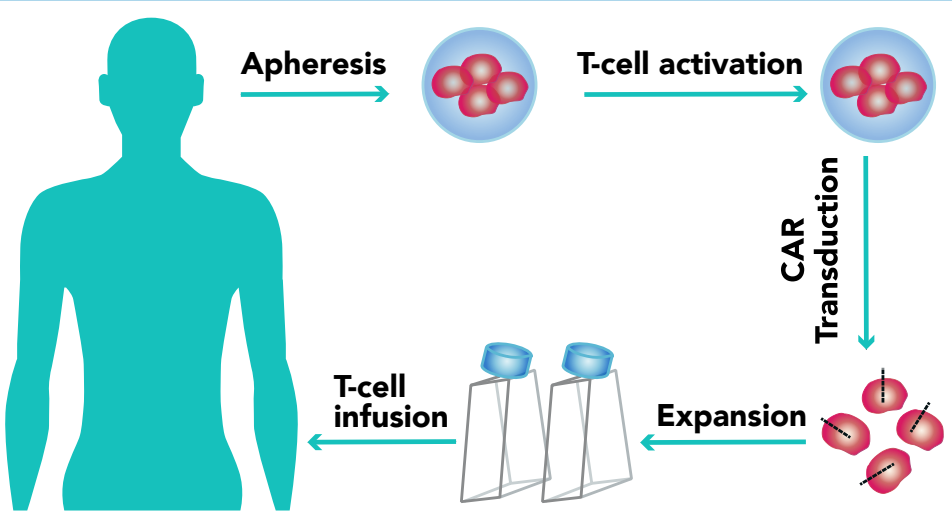
Certain protocols may include Neupogen, which is fairly controversial; we have to work on the insurance coverage for this drug and then facilitate the transition to outpatient after they have completed treatment and are out of their window of CRS toxicities.

***EBO*™: What is the duration for which patients are monitored for CRS toxicities?**

SHANK: We are more conservative in our assessment and management of these patients. When most of our patients are admitted following their conditioning chemotherapy, we monitor their ferritin and their C-reactive protein, which is an inflammatory marker used to help predict CRS. Depending on the [CAR T-cell] product that the patients have received, the time of T-cell expansion may vary following infusion. Depending on the product, we may keep the patients longer because we have to wait for the [T-cell] expansion to occur—as soon as there's expansion, that's when the CRS is most likely to occur. Other factors with possible association with CRS risk include the cell dose, extent of disease, or the patient's age.

There's also been new research out of the Fred Hutch Cancer Center [which concluded] that if a patient had a larger cell dose, high marrow tumor burden, or bulky disease, it increased the risk of CRS.

FIGURE. How Can the Pharmacy Team Help Manage a Patient Who Has Received CAR T-Cell Treatment?



CAR indicates chimeric antigen receptor.

***EBO*™: Were there specific workflow changes needed for more efficient team management of patients receiving CAR T-cell treatment?**

SHANK: I'd say that the acuity of when a CRS happens…it's an emergency, which is different from some other chemotherapy toxicity. The patient decompensate faster. Another thing that is very difficult, and for which we have systems in place, is a mechanism to avoid administration of corticosteroids. It's a common pre-med for blood products and platelets, but these [CAR T-infusion– treated] patients can't receive any, and so efforts were made to educate staff to make sure that they don't receive steroids.

As more patients undergo treatment with chimeric antigen receptor T cells, we will learn to better manage cytokine release syndrome.

Our standard admission orders needed to be altered for CAR T cells, because they include medications like zolpiderm or promethazine, which are medications that we try to avoid in this patient population.

These are some of the things we need to consider. I had one patient who was on a chronic, long-acting opioid medication, which gets tricky when you have to stop [the medication] abruptly if they have CRS, because they may develop withdrawal symptoms. So, there are many logistical barriers that are coming up now—we are learning how to manage the drugs in our arsenal when we are administering CAR T-cell infusion.

***EBO*™: Going forward, what kind of infrastructure changes would you like to see in the way CAR T-cell treatment is currently delivered in the clinic to make it easier to manage these patients?**

SHANK: One of the needs would be the capacity of the drug companies to quickly amplify the modified T cells. The financial toxicity is a problem. One article estimated the cost at between $450,000 and $475,000 per treatment. The high cost will have a significant financial impact on our healthcare system. As more patients undergo treatment, we will learn to better manage CRS. We have made great strides in the last year or two managing these patients, but we can do better and focus on risk stratification to determine which patients are at high risk.

If this proves to be the trajectory of cancer treatment, select therapies may be given in the outpatient setting or inpatient, with a potential 2- to 3-week stay. [It's] similar to a stem cell transplant, but this will be done on a lymphoma service. There's a lot that we will learn along the way, and there is a high likelihood of logistical challenges initially since a lot of patients are waiting to receive therapy.

With respect to formulary management, billing is another important question—will this treatment be billed as a medication or a blood product? What would be the role of the pharmacy? Those are some of the current unknowns with this treatment.

CAR T cells have had a profound impact and will have a tremendous impact on oncology care, for non-Hodkgin's lymphoma and leukemia. As we learn more, and more trials are available, this will be a unique treatment option for patients who have failed chemotherapy. ◆

5 Significant Developments With CAR T-Cell Therapy

Surabhi Dangi-Garimella, PhD

NOVARTIS HAS WON THE RACE to be the first company with FDA approval for its chimeric antigen receptor T (CAR T)-cell gene therapy treatment. This much-awaited approval is expected to change the paradigm for treating children and young adults diagnosed with B-cell precursor acute lymphoblastic leukemia (ALL).

Here's a look at some of the major developments in the CAR T space:

1. **Trials in solid tumors.** CAR T cells have primarily been developed for treating patients with hematological disease; however, a report published earlier this year presented a case study of the effectiveness of this leukapheresis-based treatment in glioblastoma (GBM).[1] The single-patient study treated a 50-year-old man with multiple lesions that were nonresponsive to other lines of therapy and were progressing. At a 7.5-month follow-up after the last infusion of modified CAR T cells, existing tumors were undetectable by positron emission tomography and could not be measured by magnetic resonance imaging. However, new tumors had developed.
2. **Biomarkers of response.** At the 2016 annual meeting of the American Society of Hematology, Jan Joseph Melenhorst, PhD, from the Perelman School of Medicine at the University of Pennsylvania, presented results from a study evaluating biomarkers of response to anti-CD19 CAR T-cell treatment in patients diagnosed with chronic lymphocytic leukemia. Patients with persistent functional T cells had the most durable response.[2] Transcriptomic signatures of the T cells showed that T cells from nonresponders expressed genes that regulate terminal differentiation and exhaustion. Responders had early memory T cells, which may mediate superior antitumor activity due to enhanced proliferation and survival following adoptive transfer.
3. **ODAC nod for Novartis treatment.** In mid-July, the FDA's Oncologic Drugs Advisory Committee, commonly referred to as ODAC, unanimously approved tisagenlecleucel (or CTL019) for the treatment of children and young adults with relapsed or refractory B-cell ALL.[3] The commercialization of this treatment was the result of a partnership between Novartis and the University of Pennsylvania.
4. **Tisagenlecleucel (Kymriah) approved by the FDA.** The FDA approved tisagenlecleucel in August 2017.[4] Marking this historic moment was a statement from the new FDA commissioner, Scott Gottlieb, MD: "We're entering a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer," he said. "New technologies such as gene and cell therapies hold out the potential to transform medicine and create an inflection point in our ability to treat and even cure many intractable illnesses." The FDA also approved tocilzumab (Actemra) for the treatment of CAR T-cell–induced severe or life-threatening CRS in patients 2 years and older.[5]
5. **The big question is affordability.** The treatment is expensive: $475,000. Although only a small number of patients would qualify for the current indication of tisagenlecleucel, several ongoing trials, as well as similar treatments being developed by Kite Pharma (recently bought by Gilead Sciences) and Juno Therapeutics, will soon expand the indications for CAR T-based treatments.

With this in mind, CMS is working with stakeholders to develop innovative payment agreements such as outcome-based pricing. In a statement released after tisagenlecleucel's approval, CMS Administrator Seema Verma said, "Innovations like this reinforce our belief that current health care payment systems need to be modernized in order to ensure access to new high-cost therapies, including therapies that have the potential to cure the sickest patients. Improving payment arrangements is a critical step toward fulfilling President Trump's promise to lower the cost of drugs."

"I think it's the beginning of a fascinating era in immuno-oncology," Bruce Feinberg, DO, vice president and chief medical officer, Cardinal Health Specialty Solutions, told *The American Journal of Managed Care*® in an e-mail. "Kite's CAR T [treatment] is likely to follow in 6-12 months and Juno['s] thereafter. Bluebird's product for myeloma is next in queue and shelf-stable products from folks like Cellectis move the paradigm to the next level. All of this may well happen in the next 3 to 5 years."

Feinberg feels that the current wave of CAR T therapies will have the biggest impact on relapsed and refractory hematologic malignancies: "This is a finite population for which the early-to-market companies will be competing. If the technology succeeds in primary refractory solid tumors like GBM, then it's Katie bar the door, with respect to societal cost." He added, however, that early CAR T indications will most likely compete with allogenic hematopoietic stem cell transplant (HSCT) and that "the initial Novartis price is not a far cry from aggregated allogenic HSCT cost. Therefore, I don't believe this initial price will be a significant factor in treatment adoption." ◆

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ctDNA Plus Protein Biomarker Test Allows Early Detection of Pancreatic Cancer

Surabhi Dangi-Garimella, PhD

A SINGLE BLOOD DRAW that combines the detection of DNA and protein markers could be more sensitive to earlier detection of pancreatic cancer, according to the results of a new study published in *Proceedings of the National Academy of Sciences*.[1]

With less than a 9% 5-year survival rate, pancreatic cancer is currently the third leading cause of cancer death in the United States, the primary reason being patients are typically diagnosed when the disease is at an advanced stage. Tumor size is also a significant determinant of survival: the smaller the tumor, the better the prognosis, even in the presence of metastasis to distant sites.

According to Jin He, MD, assistant professor of surgery at the Johns Hopkins University School of Medicine, early-stage pancreatic cancers are generally asymptomatic and incidental findings from an imaging scan.[2]

For the present study, the authors worked on a hypothesis that earlier detection of pancreatic cancer can successfully contribute to reducing cancer-related mortality. Toward that goal, they determined analyzing circulating tumor DNA (ctDNA) and protein biomarkers together could increase the sensitivity of detecting resectable pancreatic cancer.

The study included 221 patients with surgically resectable pancreatic cancer and 182 age-matched healthy volunteers. Twenty percent of patients had no typical disease symptoms, and the primary tumor ranged in size from 0.6 to 13 cm. The following distribution of disease stage was documented in the patients:

- Stage IA: 5%
- Stage IB: 8%
- Stage IIA: 10%
- Stage IIB: 77%

Patient blood samples were analyzed for *KRAS* mutations in the ctDNA, along with mutations in specific protein biomarkers: CA19-9, CEA, HGF, OPN, and prolactin. The study found that compared with the ctDNA test or the CA19-9 test alone, the combination assay was more successful at detecting the cancer, irrespective of tumor size.

The scientists could identify 30% of patients (66/221) with early-stage pancreatic cancer using the *KRAS* gene test alone. Adding CA19-9 to the detection strategy improved the rate of detection to 49% (109/221). However, including the remaining protein biomarkers pushed the detection rate to 64% (141/221).

"A single marker on its own won't identify early cancers in most people," said Anne Marie Lennon, MD, PhD, associate professor of medicine at the Johns Hopkins University School of Medicine and director of the Multidisciplinary Pancreatic Cyst Program, in a press release. "This study shows that it may be possible to use multiple markers to nail down the detection of early pancreatic cancer with a blood test and treat those patients earlier and better."

The authors concluded that mining genetic and protein alterations together can significantly improve the sensitivity of a blood test for early-stage pancreatic cancer. They acknowledged that excluding advanced stage (stage III and IV) patients from their study reduced the sensitivity that could be achieved, but noted that resectable cases are better suited for evaluating a screening strategy. ◆

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FDA Approves Tisagenlecleucel, the First CART-Cell Therapy in the United States

Laura Joszt

THE VERY FIRST GENE THERAPY is coming to the United States. The FDA approved tisagenlecleucel (Kymriah), the chimeric antigen receptor (CAR) T-cell treatment, for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL) in certain pediatric and young adult patients. The therapy is developed by Novartis.

"We are so proud to be part of this historic moment in cancer treatment and are deeply grateful to our researchers, collaborators, and the patients and families who participated in the Kymriah clinical program," Bruno Strigini, CEO of Novartis Oncology, said in a statement.[1]

CAR T-cell therapy represents a novel way to treat cancer: the treatment reengineers a patient's own white blood cells to attack tumor cells.

"We're entering a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer," FDA commissioner Scott Gottlieb, MD, said in a statement. "New technologies, such as gene and cell therapies, hold out the potential to transform medicine and create an inflection point in our ability to treat and even cure many intractable illnesses."[2]

Each dose of tisagenlecleucel is customized using the individual patient's own T cells, which are sent to a manufacturing center to be genetically modified. The new cells include the *CAR* gene, which directs T cells to target and kill leukemia cells with the CD19 antigen on the surface. The cells are then infused back into the patient.

"Kymriah is a first-of-its-kind treatment approach that fills an important unmet need for children and young adults with this serious disease," said Peter Marks, MD, PhD, director of the FDA's Center for Biologics Evaluation and Research. "Not only does Kymriah provide these patients with a new treatment option where very limited options existed, but a treatment option that has shown promising remission and survival rates in clinical trials."

At the beginning of July, the FDA's Oncologic Drugs Advisory Committee had voted unanimously in favor of tisagenlecleucel.[3] A trial of 63 patients with relapsed or refractory B-cell precursor ALL reported an 83% remission rate within 3 months of treatment. CAR T-cell therapy can cause cytokine release syndrome (CRS), which is a response to the activation and proliferation of CAR T cells and manifests as high fever and flu-like symptoms. Tisagenlecleucel will also carry a boxed warning for neurological events.

In an interview at last year's Patient-Centered Oncology Care® meeting, David L. Porter, MD, of the University of Pennsylvania Health System, explained that CRS is the most serious side effect of CAR T-cell therapy.[4] "It almost always starts with a fever and can escalate over time to very, very severe flu-like syndrome, with other complications," he said. "Patients will have progressively high fevers, they can get as high as 104°, 105° and even higher. And as this progresses, patients develop myalgias and arthralgias, muscle aches and bone and joint aching that really has been quite severe in some cases."

The FDA has approved a treatment for CAR T cell–induced CRS: tocilizumab (Actemra) was approved to treat CRS in patients 2 years or older. ◆

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Mammography Device Approved by FDA Gives Patients Control Over Pressure Levels

Christina Mattina

THE FDA HAS APPROVED THE FIRST 2D digital mammography system that lets patients adjust the level of compression applied to their breast during the imaging procedure.

Mammograms are a key tool in detecting breast cancer, but some women report discomfort with the procedure, which requires the breast to be compressed in order to capture a 2D x-ray image. The new device could »

potentially expand uptake of mammograms by empowering patients and making the experience more comfortable.

According to the FDA announcement, the Senographe Pristina with Self-Compression, manufactured by GE Healthcare, was approved through the premarket 510(k) pathway.[1] GE had to demonstrate that the new device is clinically equivalent to the Senographe Pristina, an approved digital mammography device that allows the technician operating the device full control over compression.

The self-compression device differs from the original machine by including a wireless remote control held by the patient that can adjust the compression force. After the technologist positions the patient's breast, the patient is asked to use the remote control to gradually increase the level of compression to a point she finds tolerable. The technician then checks whether the compression is sufficient to achieve a clear image and can adjust it if necessary.

"This device allows patients some control over the amount of compression for their exam."

—Alberto Gutierrez, PhD

Trials conducted as part of the premarket approval process confirmed that allowing patients to control compression with the remote control did not diminish image quality compared with the device now in use. The average time of the mammogram did not increase either. The finding that the new device was at least as safe and effective as the approved device contributed to the FDA's decision to grant premarket clearance to GE.

"Regular mammograms are an important tool in detecting breast cancer. However, some patients may experience anxiety or stress about the discomfort from the compression during the mammogram," said Alberto Gutierrez, PhD, director of the Office of In Vitro Diagnostics and Radiological Health at the FDA's Center for Devices and Radiological Health, in the announcement. "This device allows patients some control over the amount of compression for their exam."

This sense of control, along with reduced pain and discomfort, could have significant implications for changing women's perceptions of mammography and their willingness to undergo screening. A 2013 review published in *The Breast* showed that between 25% and 46% of women who did not return for subsequent mammograms cited pain during the initial mammogram as the reason.[2] ◆

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FDA Emphasizes Risks of Pembrolizumab in Multiple Myeloma After Reviewing Halted Trials

Christina Mattina

LESS THAN 2 MONTHS AFTER it ordered a stop to 3 trials of pembrolizumab (Keytruda) in multiple myeloma due to safety concerns, the FDA has released a more detailed analysis of what went wrong in the trials.

Merck, which developed pembrolizumab, announced in July that the FDA had placed 2 phase 3 studies on full hold and a phase 1 study on partial hold, citing a pattern of patient deaths.[1] The FDA's safety alert, issued recently to healthcare providers, oncology researchers, and the public, analyzes data from the 2 phase 3 trials that were halted completely.[2]

KEYNOTE-183 had been studying pembrolizumab in combination with pomalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma. KEYNOTE-185 was assessing pembrolizumab in combination with lenalidomide and low-dose dexamethasone in those with newly diagnosed and treatment-naïve multiple myeloma.

KEYNOTE-183 documented 29 deaths in the investigational arm receiving pembrolizumab and 21 deaths in the control arm. The FDA determined that the relative risk of death was 61% higher for participants in the pembrolizumab arm. This increased hazard was not accompanied by improved outcomes, as the objective response rate was 34% in the investigational arm and 40% in the control group. Patients receiving pembrolizumab were also more likely to experience a higher rate of grade 3 to 5 toxicities than their counterparts in the control arm (83% vs 65%, respectively), as well as serious adverse events (63% vs 46%). The most common causes of death unrelated to cancer progression in the pembrolizumab arm included several heart-related conditions, neutropenic sepsis, and multiple organ dysfunction.

The KEYNOTE-185 trial appeared to pose even more risk to participants. There were 19 deaths in the investigational arm and 9 in the control group, indicating a risk of death that was over 2-fold for the patients receiving pembrolizumab. Higher incidences of grade 3 to 5 toxicities (72% vs 50%) and serious adverse events (54% vs 39%) were observed in the pembrolizumab arm than in the control arm.

Noncancer causes of death in the investigational arm of KEYNOTE-185 included the cardiac events seen in KEYNOTE-183, intestinal ischemia, suicide, and sudden death. The objective response rate in the pembrolizumab arm was 64%, compared with 62% seen in the control arm.

Both the data analysis and a press statement[3] from the FDA emphasized that these safety risks only apply to multiple myeloma, which is not an approved indication of pembrolizumab, and that patients taking the drug for approved indications—which include melanoma, lung cancer, head and neck cancer, classical Hodgkin lymphoma, and others—should continue to do so.

"Today's alert underscores the importance of why new therapies are thoroughly studied to ensure the benefits of taking them outweigh the risks to patients, and we will continue to aggressively monitor clinical trials to ensure patients are protected when safety concerns arise," said Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research, in the announcement. ◆

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Race, Socioeconomic Status Linked to Rehospitalizations Among Patients With Advanced Cancer

AJMC® Staff

A NEW STUDY IN the *Journal of Clinical Oncology* identifies an increased role for physicians in boosting human papillomavirus (HPV) vaccination rates among childhood cancer survivors to reduce their risk of a second cancer.[1]

The study surveyed 982 childhood cancer survivors (the majority of whom were leukemia/lymphoma survivors), aged 9 to 26 years, who had completed treatment between 1 and 5 years prior to the survey. The survey touched on:

- Whether they had received an HPV vaccine
- Whether their provider had recommended the vaccine
- Their attitude toward vaccination

The results drawn on the HPV vaccination rates were compared with the vaccine initiation rates in the general population. More than a 1.5-fold difference was noted between the 2 populations: a 24% vaccination rate among the childhood cancer survivors compared with 40% in the general-population peers. Males, overall, were more likely to get vaccinated.

The biggest difference, the study noted, was among teens 13 to 17 years of age: 22% for cancer survivors compared with 42% for their general population peers. However, the numbers were on par in the older population (18 to 26 years old): 25% for survivors and 24% for their generalpopulation peers.

With nearly 7 million adolescents and young children infected with HPV annually, the virus has a significant bearing on the incidence of cervical cancers and many oral, anal, vaginal, vulvar, and penile cancers. Childhood cancer survivors are particularly susceptible to HPV infection due to their already weakened immune system post cancer treatment. This has led organizations, like the American Society of Clinical Oncology, to recommend that girls and boys should be vaccinated against HPV to reduce the incidence of cancer.

"This study shows that an effective, affordable, and widely available tool for cancer prevention is being underutilized by survivors of childhood cancer."

—James Klosky, PhD, ABPP

The current study identified lack of physician recommendation as being the biggest barrier to vaccination: 72% did not get a recommendation and only 5% of those surveyed ended up getting vaccinated. The most important finding was, of the 28% who received a recommendation from their physicians, more than half got vaccinated.

"This study shows that an effective, affordable, and widely available tool for cancer prevention is being underutilized by survivors of childhood cancer," said study author James Klosky, PhD, ABPP, an associate member at St. Jude Children's Research Hospital in Memphis, Tennessee, in a statement. "As clinicians, we need to initiate more conversations about HPV vaccination, especially with childhood cancer survivors, because they stand to benefit even more than their peers."

Next, Klosky said, researchers must develop interventions that ensure clear communication between a patient's survivorship and primary healthcare teams, so that appropriate measures are in place for care continuity. ◆

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Financial Concerns Influence Care-Seeking Behavior of Childhood Cancer Survivors

Surabhi Dangi-Garimella, PhD

HIGH OUT-OF-POCKET (OOP) medical costs in survivors of childhood cancer can influence their treatment choices and care-related behavior and ultimately affect their health outcomes. This was the conclusion of a study that evaluated the prevalence of financial burden in this patient population.[1]

High treatment costs, particularly for diseases that require long-term follow-up or long-term care, can be a financial strain for patients. Studies have shown that financial burden in adult patients with cancer can prove a negative influence on outcomes, including their quality of life, symptom burden, and survival. In the current study, the authors queried whether survivors of childhood cancer experience a financial burden and is this associated with high OOP costs and alterations in the patients' lifestyle or care-seeking patterns.

The authors studied an age-stratified sample of childhood cancer survivors (n = 580) and used their siblings as a comparison group (n = 173). The survivor pool, which included patients who had enrolled in the Childhood Cancer Survivor Study—a longitudinal follow-up that compares health outcomes of survivors of childhood cancer with those of siblings—shared their household income, OOP medical costs, and issues related to financial burden. The 580 participants who shared their financial information were more likely to be married and to have higher education and higher household incomes compared with the original 1101 survivors that the authors had selected for this study.

Compared with their siblings, survey participants were:

- Male (46.7% vs 37.1%; $P = .025$)
- Unmarried (35.4% vs 24.6%; $P = .008$)
- Had severe to life-threatening chronic medical conditions (39.7% vs 17.1%; $P < .001$)
- Have Medicare (5.8% vs 1.1%; $P = .011$) or Medicaid/state insurance (11.5% vs 4.6%; $P = .008$)

Survivors of childhood cancer were more likely to have OOP medical costs that were 10% or higher of their annual income compared with 2.9% for the sibling ($P < .001$). The primary reason for higher OOP spending was hospitalization in the past year (OR, 2.3; 95% CI, 1.1-4.9) and annual household income less than $50,000 (OR, 5.5; 95% CI, 2.4-12.8). Additionally, higher OOP spending had a significant association with:

- Problems paying medical bills (OR, 8.9; 95% CI, 4.4-18.0)
- Deferring care for a medical problem (OR, 3.0; 95% CI, 1.6-5.9)
- Skipping a test, treatment, or follow-up (OR, 2.1; 95% CI, 1.1-4.0)
- Thoughts of filing for bankruptcy (OR, 6.6; 95% CI, 3.0-14.3)

The survey results showed a strong association between survivors with a high OOP medical spend and financial burden, the authors note. More importantly, although survivors were an average 30 years from their cancer diagnosis, many continued to struggle with OOP medical costs and their associated financial burden.

The authors believe that their study, which identified characteristics of the most financially vulnerable patients, can be used to proactively target specific patients at high risk of financial burden.

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What Is the Ideal Age for Screening Mammography?

Surabhi Dangi-Garimella, PhD

THE CONFLICT OVER THE RECOMMENDED age for a screening mammogram continues with a new study whose authors conclude that an annual screening starting at age 40 has the greatest impact on reducing mortality.[1]

The study used mean values from 6 Cancer Intervention and Surveillance Modeling Network (CISNET) models to compare 3 recommendations from major healthcare organizations:

- Annual screening at ages 40 to 84 years
- Screening annually at ages 45 to 54 years, then biennially at ages 55 to 79 years
- Biennial screening at ages 50 to 74 years

Per their analysis, the highest reduction in mortality was observed in the cohort that started annual screening at age 40 and continued until age 84 years (mean reduction, 39.6%). The second highest mortality reduction was observed in the hybrid group (mean reduction 30.8%)—this group initiated their annual screening at age 45 and continued until age 54, followed by biennial screening from 55 to 79. The group that followed the biennial screening recommendation between 50 to 74 years had the lowest reduction in mortality (23.2%).

The analysis showed that for a single-year cohort of women aged 40 years, an annual screening mammogram initiated at age 40 would prevent 29,369 deaths. This compared with 22,829 lives saved due to the hybrid screening and 15,599 lives from the biennial screening (based on 2016 CISNET estimates).

The study conducted a head-to-head comparison of 3 widely discussed recommendations for screening mammography.

"Our findings are important and novel, because this is the first time the 3 most widely discussed recommendations for screening mammography have been compared head-to-head," senior author Elizabeth Kagan Arleo, MD, of Weill Cornell Medicine, said in a statement. "Our research would be put to good use if, because of our findings, women chose to start annual screening mammography starting at age 40. Over the long term, this would be significant because fewer women would die from breast cancer."[2] Arleo would like women and their physicians to use the findings of this analysis to guide screening choices with respect to initiation and frequency of screening.

In an accompanying editorial, Otis Brawley, MD, FACP, chief medical officer of the American Cancer Society, highlighted the importance of an individual's value judgement.[3] "Our goal should be to provide truthful, balanced information so that women can make informed choices about when to start screening for breast cancer. A woman who is making a decision about screening is more interested in her personal chances of benefit and risk of harm and is less interested in the benefits to the population," he wrote.

His editorial also pointed out the limitations of a mammogram and emphasized the importance of a better test for women that would avoid false positives and be more sensitive. ◆

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5 Takeways for Payers, Providers From the NCCN Meeting on Quality Metrics

AJMC® Staff

THE NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) chose a very appropriate topic for this year's policy meeting: Redefining Quality Measurement in Oncology. While "measure, measure, measure" has been the mantra in healthcare, defining what, when, and how to measure remains a challenge. However, with value-based care and alternative payment models experimenting with identifying appropriate quality measures, defining the right metric has become more urgent than ever.

Following are a few takeaways from the NCCN summit, which was held September 25, 2017, in Washington, DC.

1. **A voice for the patient.** Ronald Walters, MD, MBA, MHA, MS, associate vice president of medical operations and informatics, The University of Texas MD Anderson Cancer Center, said that the value-based care movement has finally moved away from being provider-centric to being patient-centric. While provider-centric measures of care are important, patient-centric measures of value, including patient experience (eg, satisfaction), engagement, and outcomes, are vital, he said.
2. **Quality for whom?** During her presentation, Mary Lou Smith, JD, MBA, cofounder, Research Advocacy Network, asked who was at the receiving end of the quality measures: the care provider, the patients, or the healthcare system? "Patients know when they have answers to their questions, but patients don't know what questions to ask," Smith said. This then pushes the onus on the stakeholders responsible for patient care to identify the right measures that can ensure good health outcomes.
3. **Challenges with identifying the right measures.** On a panel that saw representation of patient advocates, oncologists, health policy researchers, health plans, and the pharmaceutical industry, the discussion revolved around ways to gather the right evidence for quality measurement to improve outcomes. "We don't just have to measure everything, but we do need to understand the accuracy of what we are measuring. We definitely need a quality measure to understand patients' comprehension of their treatment and disease," said John Fox, MD, MS, medical director, Priority Health. Panelists agreed, however, that accountability for quality care rests on all stakeholders.
4. **Best practices in quality measurement.** Kerin Adelson, MD, medical oncologist, Yale Cancer Center/Smilow Cancer Hospital, presented her research on how their health system grappled with teasing out the right structured and unstructured data in collaboration with Flatiron Health. She pointed out that while provider attribution is hard, particularly when mapping out care delivered to a patient in the oncology space, they have been using information extracted via Flatiron's technology platform.

   "Provider level view will lead to change," Adelson said, adding that their research team plans to develop national benchmarks for quality using Flatiron's database.
5. **Looking to the future.** Adelson then sat on a panel with Basit Chaudhry, MD, PhD, Tuple Health; Joanne Buzaglo, PhD, Cancer Support Community; Virginia Calega, MD, MBA, Independence Blue Cross; Peter Ellis, MD, University of Pittsburgh Cancer Institute; and Marcus Neubauer, MD, McKesson Specialty Health. The experts discussed how providers in the community and health systems are working in tandem with health plans and technology companies to navigate the maze of value-based care.

Panelists agreed that healthcare providers cannot shy away from changes within our care delivery system and that they need to keep up with the dynamic nature of payment reform. ◆

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Produced by Laura Joszt and The Center for Biosimilars®

Amanda Forys on How Medicare Will Refine Its Biosimilar Policy

Amanda Forys, MSPH, director of Xcenda's Reimbursement Policy Insights consulting team, discusses how Medicare will address and possibly change its biosimilar policies as the FDA offers more guidance and as biosimilars become more prevalent in the market.

How do you think Medicare may refine its biosimilars policy as the FDA releases more guidance and more biosimilars reach the market?

FDA guidance could affect a little bit of what Medicare is doing. The FDA and CMS are going to have some lessons learned moving forward. There are a lot of other really big issues coming up around the Medicare program in general, that could affect biosimilars and could affect all products. A couple of those things, I believe, are going to be hot-button issues, but I'll start with just biosimilars in general.

Right now, with a biosimilar, the originator product has its own billing code and all biosimilars to that originator product are grouped together into a billing code. In the industry, a lot of members of different biosimilar forums and other councils for biosimilars have not been interested in keeping it that way and have been working very hard to ask that they each get their own code. They're saying that these are products that are each unique, they are not biosimilar to one another, so grouping them together is quite confusing for providers and was not necessarily the intent of the BPCIA [Biologics Price Competition and Innovation Act] when that legislation was passed. There is a lot of tension there with CMS and people asking for them to split the codes up.

Then you have MedPAC coming in and they are saying we want to simplify the whole system and what we'd like to do is we'd like to see the originator product and the biosimilar grouped together and share a code. When that happens, you are going to see the price of that originator product drop substantially and that will really save the Medicare program money. While, in theory, yes that probably could save money, the intent of the BPCIA isn't necessarily clear, and that may not be possible, it might not be something you can do legally, by grouping those products together with the way the biosimilar is defined. That's going to be something that has to be ironed out and you may see some guidance as interchangeables come to the market and the FDA irons out interchangeables you might see them say, how are we going to treat that? Are we going to give that its own code, its own separate billing code? Are they going to be grouped with all of the other biosimilars? Will they even share a code with the originator product because they are an interchangeable? We just don't know yet. That is something that could be a concern or an issue for biosimilar manufacturers. It's just really ironing out payment.

Also, to see some of the other pressures to control drug prices, that's a huge hot topic right now on [Capitol] Hill. Are you going to see CMS suing significant things to change the average sales price base payment methodology that they have for Medicare Part B drugs? Could that happen and, if so, how will that affect the market? I think you've got what's happening in general and then how will that affect biosimilars, just as much as how is the biosimilars market going to change. On the Part D side, we are definitely going to need to see more clarification on [whether] a biosimilar can be considered a brand, that is something that manufacturers are looking for and asking for that clarification, so that they can offer that 50% rebate in the coverage gap for patients. So, that is something that will be defined more and more. MedPAC has recommended that be put in place, so we will see if that actually happens in the future. ◆

Dr Brandon Shank on Biosimilar Naming and Suffixes

Brandon Shank, PharmD, MPH, BCOP, clinical pharmacy specialist, discusses the merits of the current biosimilar naming system.

Could 4-letter suffixes to the names of biosimilars create confusion?

One benefit of the naming system is that you know what the reference product is. Some clinicians, pharmacists included, and patients may assume interchangeability, which may not be inferred by the naming system. It is important to have a way to differentiate these products so that you can know which ones are interchangeable, so that ones with different indications will also be recognized and not be used for the wrong indication. Also, dosing and administration differences in products may also be assumed with the naming system, which is why the suffix will be helpful in those situations. I also believe that with this naming system, they need to differentiate the products in the computer order systems and be able to have adverse event reporting that distinctly identifies them, which the naming system will with the current suffix system. ◆

Kim Woofter: Data at Point of Care Necessary for Success in Value-Based Models

As the healthcare industry moves increasingly toward value-based payments, practices have a greater need for usable data that can help them succeed in new payment models, said Kim Woofter, executive vice president of strategic alliances and practice innovation at the Advanced Centers for Cancer Care, at OncoCloud '17, held by Flatiron Health September 16-17, 2017, in Las Vegas, Nevada.

What are the main challenges to implementing value-based payments in oncology?

So many practices do not know exactly what it costs for them to deliver that care, so they can't get into value-based care if they don't truly know what it costs them. There's too much risk involved. And, so, organizations, such as Flatiron Health, [provide] some of the consolidation of data and the ability to look at your patient base over a continuum, so that you can actually go into a value-based model with information or well informed, and that will help you to be successful.

How can practices ensure that all the data they are receiving and have access to are being used at the point of care?

That's a really good question, because to use data at the point of care, it has to be cleansed and streamlined and it's a very difficult task to get into the hands of a provider. It takes a larger organization with some real knowledge about the workflow of a practice to actually make that happen. I think you're seeing that in some of the Flatiron tools that are being developed right now. ◆

Dr Kashyap Patel Discusses Biosimilars and Medicare Part D Drug Pricing

Kashyap Patel, MD, medical oncologist, Carolina Blood and Cancer Care, highlights the potential impact of biosimilar drugs on Medicare Part D drug pricing.

What would be the impact of biosimilars on Part D drug pricing?

So right now, our country is facing a drug price explosion. There's been a couple of areas where it's growing fastest—the hematological space, where we're growing about 12.9% per year in terms of cost, and in the oncologic space, [which is] growing at 4.9%. So, we don't have infinite resources, and at some stage, the system with either implode, or we have to look at drug pricing. Biosimilars do have a role. They can help in reducing some of the additional escalation of the expenses. When we go back and look at the European experience, in Europe, in 10 years' time, drug prices have dropped by about 30% compared to the reference product. So clearly biosimilars do have a significant role that they can play in the Part D drug pricing space, and they also improve access as well, so biosimilars have a very valid and legitimate space in becoming part of the solution for Part D prices. ◆

Robert Cerwinski on Healthcare Reform and the BPCIA

If the Affordable Care Act, the ACA, is repealed, what becomes of the Biologics Price Competition and Innovation Act (BPCIA)?

So, the BPCIA is part of the ACA, and if Congress repeals it lock, stock, and barrel, without having some replacement ready to go, technically the BPCIA goes with it, right? I don't think any of us expect that that's going to happen, but I'll tell you that with the current administration and with the current Congress, uncertainty seems to be the rule. The BPCIA so far, in all the debate that we have been hearing and monitoring in Congress and in the administration, seems to be flying completely under the radar. It does not appear to be one of the controversial aspects of Obamacare that the president and Congress are really focused on.

From that standpoint, that's good for biosimilar applicants, but again, because there is this uncertainty, we have at least been watching it. I think I can say that nobody really expects the BPCIA to go away, and we don't think it is seriously at risk, but certainly we watch what Congress is doing in this respect. ◆

Dr Bruce A. Feinberg: Biosimilar Labeling and Extrapolation

What are some considerations in the labeling of biosimilars?

The biggest consideration in biosimilar labeling is the fact of extrapolation. Extrapolation relates to the fact that a biosimilar that may have a half-dozen specific disease indications, will likely only be clinically tested in 1 of those indications. If it is proven to be equivalent by all the different measures the FDA is using, then the FDA appears to be granting, by extrapolation, the expanded label to all indications. So, there is a big difference from a branded drug, which had to have clinical trials in each of the 6, to a biosimilar which is only going to have a clinical trial done in 1 of the 6. ◆

Dr Lee Newcomer on Policy Decisions as New Immunotherapy Agents Are Developed

Lee N. Newcomer, MD, MHA, senior vice president of oncology and genetics at UnitedHealthcare, discusses off-label communications and how coverage determinations are changing along with the production of new immunotherapy agents.

How are coverage determinations being made for newer immunotherapy agents? Are policies being developed for CAR T-cell treatments?

Our policy about making decisions on new technology has never changed. In cancer, we rely on the National Comprehensive Cancer Network [NCCN] guidelines, and so that decision is made actually external to UnitedHealthcare by about 25 of the world's leading cancer centers. If they tell us there's enough evidence to approve it, we approve it. CAR T won't be any different, nor will the new immunotherapies.

You need to develop evidence, the professionals need to recommend them based on that evidence—and that's how we decide. The one thing about CAR T is that it's going to be very expensive. Those therapies will cost anywhere from half a million to $2 million per treatment, and so we are organizing both to provide the financing for that and to make sure that the right centers provide that care.

What kind of off-label information would prove useful for payers? What do you think is the impact of off-label communications?

Well again, we rely on the NCCN, so there's plenty of evidence sometimes for off-label indications. In fact, most of the indications for cancer are off-label, but we're looking to the NCCN to weigh the evidence to support it. So, it's their call but the more studies you do and the stronger the studies are, the more likely you are to get a recommendation from the NCCN.

What have been some lessons learned as United Health has implemented value-based contracts with providers? And how is the data you gather being used?

Well, all of this is hard work. The first lesson is, you really do need to half a good comparison database and we've spent almost 8 years building that database. So, we now have fee-for-service patients where we have clinical information, enough so that we can match the patients that are being cared for by a medical group in our episode program. If we can do that exact match, then we can compare apples to apples, rather than apples to oranges and it makes for a much fairer comparison and more accurate results. But, building the database it tough.

I think the other big barrier is that physicians and practices have never had internal data systems—they don't know how to measure their own performance. When we put them at risk, one of the things they learn very quickly is that they need better information inside their practices. We're helping with that by providing them claims data to help with that area, but it's not enough to do that just alone. All of us are learning as we go through this experience, and the good thing is that patients are getting better care because of it.

What work do you do with physicians to help them implement things like episode-based payments and educate them?

An episode payment is partnership; we both have the same incentive now. The more we can bring cost down and improve quality, the more we both win. The physicians will make more money and our patients are better served. So, rather than have a conflict here, that we do in fee-for-service, we now have a partnership where we are bringing them data from the claims system to show them what they could do differently. We are bringing them comparison data from other groups to show who's got maybe a better way of solving a problem. We bring them together every year for a round-table discussion to look at that data and talk among ourselves about what our best practice is. Partnership is key and we are now working together because we have the same common goal. ◆

Formulary Considerations: The Past, Present, and Future

Molly Billstein Leber, PharmD, BCPS, FASHP

BILLSTEIN LEBER

Molly Billstein Leber, PharmD, BCPS, FASHP, is manager, Medication Policy and Formulary Management, Yale New Haven System.

continued from cover

A formulary agent may be restricted or unrestricted, with restrictions defined by indication, service, or specialty group (eg, infectious disease); medical staff hierarchy (eg, attending only), or patient population (eg, cystic fibrosis, pediatric). Off-criteria uses of formulary agents constitute a nonformulary use. Ideally, medication utilization evaluations should be conducted on a regular basis to assess compliance with formulary restrictions. When multiple agents within a therapeutic category are available on the market (such as low-molecular weight heparins or histamine-2 receptor antagonists), drug class reviews are often conducted in an attempt to declare therapeutic equivalence and maintain only 1 preferred agent on the formulary. An increasing number of medications within a therapeutic category can lead to greater price variation among the medications, which creates potential for significant cost savings through declaring agents therapeutically equivalent and allowing them to be interchanged.

In addition to cost savings, patient safety is enhanced by minimizing look-alike sound-alike medications through streamlined inventory and the medication reconciliation process. Minimizing the number of agents available on a formulary also improves staff competency and knowledge about specific medications.

Selecting an agent for inclusion in a formulary requires numerous operational considerations:

- With respect to purchasing, it is important to determine if a drug is supplied by the organization's pharmaceutical distributors or if it is a specialty/limited-distribution drug requiring direct shipment. Not all pharmaceutical wholesalers are able to supply the drug product, particularly high-cost specialty medications. Since most pharmacy departments purchase products from wholesalers at a cost minus discount, the pharmacy will be charged a higher price if the drug being reviewed comes from another source, potentially resulting in a significant increase in drug expenditures due to the loss of the cost-minus discount. Manufacturers can switch between different distribution strategies to best fit the needs of patients and providers as the marketplace changes.

- Drugs with a limited distribution are not shipped as frequently as deliveries from wholesalers. Under these circumstances, additional storage space may be needed, such as a refrigerator or a freezer, to ensure timely patient care. Packaging of the pharmaceuticals is also important to take into consideration, especially with increased usage of barcode medication administration (BCMA). BCMA can improve medication safety by verifying that the right drug is being administered to the right patient. BCMA technology has been proven to reduce medication administration errors.[2,3] To ensure BCMA is being used effectively, compliance rates should be evaluated regularly and any potential barriers to compliance should be investigated.

Pharmacy and Therapeutic committees play a vital role in ensuring safe, appropriate, and cost-effective use of pharmaceuticals for patients.

Often, the barrier identified is the lack of a barcode. The FDA currently requires barcodes on containers, but does not require that unit dose containers be available for all medications. Since not all manufacturers provide barcoded unit-of-use dosage forms, pharmacies are often required to prepare dosage forms through automated repackaging equipment. The barcodes are also used to ensure the correct drug is loaded into the automated dispensing cabinet (ADC) and in compounded sterile products (CSP)—all in an effort to improve patient safety. Technology-assisted CSP preparation uses computerized workflow processes that require barcode scanning of containers and ingredients.

The stability of the CSP also plays a role in formulary management. For medications that require refrigeration, the refrigerator must be connected to an ADC on the patient care unit where the patient room is located. Ensuring there is space to appropriately store the medication is crucial; size and product classification determine storage conditions and how medications can be dispensed. ADCs ensure secure storage of drugs, but require careful inventory management so that all of the needed drugs in adequate quantities are available for patient use. Compliance with USP <800> is vital to determining what drugs can be stored in an ADC or compounded at the organization. USP <800> describes hazardous drug handling related to the receipt, storage, compounding, dispensing, administration, and disposal of both sterile and nonsterile products and preparations.[4]

Drug Cost and Reimbursement

When selecting a preferred formulary agent, the cost of the drug and the reimbursement amount should also be considered. However, the cost of a drug should only be considered after its clinical efficacy and safety are established. For health systems that are 340B-eligible, providing a competitive 340B price is critical to the

formulary decision. Created by Congress through the Veterans Health Care Act of 1992, 340B is a drug discount program that allows safety-net providers with large shares of low-income patients to access discounted drug pricing.[5]

Reimbursement should also be an important consideration in the formulary evaluation. For hospitalized patients (in-patients), drugs are reimbursed as part of a Diagnosis-Related Group (DRG), so the best-priced product is the preferred product. However, on the outpatient side, the price of the product is as important as the reimbursement. With rising medication costs, pharmacy benefit managers are increasing the number of tiers in a formulary, changing co-payment structures, and dictating the brand, where, and how patients can receive their medications. These decisions often conflict with the final hospital formulary decision and require a routine audit process to compare the actual reimbursement with what was projected. Insurance companies often change their preferred formulary agent to match changes within pricing structures or rebates.

In addition to cost savings, patient safety is enhanced by minimizing look-alike, sound-alike medications through streamlined inventory and the medication reconciliation process. Minimizing the number of agents available on a formulary also improves staff competency and knowledge about specific medications.

Protocol to Incorporate Formulary Changes

When planning for formulary additions and changes, the medication's integration into technology should be carefully coordinated:

- Dosage forms, concentrations, and ordering options should be limited and standardized.
- Required monitoring for efficacy and toxicity should be built into computerized prescriber order entry (CPOE) panels or sets whenever possible.
- If a drug is infused through a smart pump, it should be programmed with a standardized concentration and volume and the appropriate limits.
- All formulary drugs should be available for ordering in the CPOE system, minimizing the need for verbal orders.

In addition to the clinical and operational considerations necessary for formulary evaluation, the focus of health systems has changed. Healthcare organizations now focus on value-based reimbursement models and participating in accountable care organizations. These changes are simultaneously forcing P&T committees to change. There has been a transition to ensuring compliance with regulations and meeting publicly reported quality metrics.[6] P&T committees have also expanded their focus to include the oversight of CPOE and the associated medication orders and order sets and building the necessary clinical decision support. However, the most significant change in healthcare that has impacted P&T committees and formulary management is the focus on cost containment and reimbursement while being able to provide high-quality patient care. As the healthcare payment structures continues to change, the structure and oversight of P&T committees will continue to transform, too.

Oncology Drugs

One of the most notable drivers of this change is the high cost and complicated treatment regimens of oncology drugs. It is now essential for health systems to, in addition to input from the medical staff, consider the patient mix and chief insurance provider when making a formulary decision. To make this transition, P&T committees will need to transform how they have historically conducted business.

Traditional drug monograph reviews are solely based on safety, efficacy, and acquisition cost. After a request for formulary addition is received, the monograph is created by a clinical pharmacist and reviewed by physician stakeholders. The recommendations are often based on a published consensus statement or guideline, which may not consider the overall cost within the recommendation. In the future, health systems will be looking at P&T committees to take different factors into consideration to determine how best to utilize drugs to provide the most value to their patients, weighing efficacy, safety, cost, and outcomes.

Cancer care accounts for 5% of total US healthcare costs, and these costs continue to rise. Estimates suggest that the annual rate of spending will rise to $158 billion in 2020 from $120 billion in 2010, and the expenditures for oncology drugs are rising more rapidly than any other facet of healthcare.[6] There continues to be an increasing financial burden associated with chemotherapeutic agents. The rising cost of cancer treatment is a significant contributor resulting in personal bankruptcy.[7]

To start the discussion around value and to determine the best way to include pharmacoeconomic analyses into formulary management, several initiatives have been undertaken in an attempt to define the value of drugs used for cancer care, including the American Society of Clinical Oncology's Value Framework, the European Society of Medical Oncology's Magnitude of Clinical Benefit Scale, the National Comprehensive Cancer Network's Evidence Blocks, Memorial Sloan Kettering Cancer Center's Drug Abacus, and the Institute for Clinical & Economic Review's Value Assessment Framework. These frameworks display similarities, but differ in their purpose, focus, and means of assessment. The final objective of all of these initiatives is to assist with the assessment of value in cancer care; however, most of these frameworks are relatively new and a significant amount of work remains to be done to determine how best to integrate these assessments into the ultimate formulary decision.[8-12]

Although the costs of drugs continue to rise, the question of the relative value of the drug itself is left unanswered by our current healthcare system. We cannot continue to review drugs in silos based only on safety, efficacy, acquisition costs, and outcomes. Healthcare systems also need to be aware of all the current regulations and intricacies of their CPOE system to ensure safe delivery of drugs that are added to the formulary. ◆

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"We have some unfinished business."

INDICATION

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

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.

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

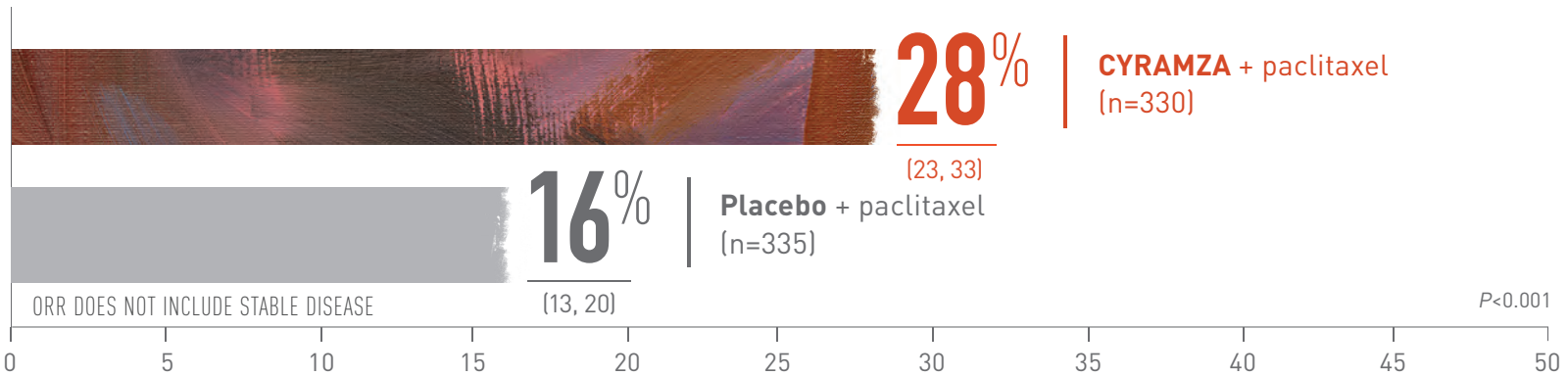
"I'm in this for as long as I can be."

For patients with advanced gastric or GEJ adenocarcinoma with disease progression after prior fluoropyrimidine- or platinum-containing chemotherapy

Adding CYRAMZA to paclitaxel nearly doubled the response vs paclitaxel alone[1,2]

ORR (Complete and Partial Response): Supportive Outcome Measure

RAINBOW ORR: percent of patients (95% CI)[1]



- Disease progression and tumor response were assessed by investigators in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1[2]

CYRAMZA plus paclitaxel significantly extended OS and PFS[1]

Overall Survival: Major Outcome Measure (95% CI)

CYRAMZA + paclitaxel (n=330): **9.6** MONTHS* (8.5, 10.8)

VS

Placebo + paclitaxel (n=335): **7.4** MONTHS* (6.3, 8.4)

Hazard ratio=0.81 (0.68, 0.96); *P*=0.017

- The percentage of deaths at the time of analysis was 78% (256 patients) and 78% (260 patients) in the CYRAMZA plus paclitaxel and placebo plus paclitaxel treatment arms, respectively

PFS: Supportive Outcome Measure (95% CI)

CYRAMZA + paclitaxel (n=330): **4.4** MONTHS* (4.2, 5.3)

VS

Placebo + paclitaxel (n=335): **2.9** MONTHS* (2.8, 3.0)

Hazard ratio=0.64 (0.54, 0.75); *P*<0.001

- The percentage of events at the time of analysis was 85% (279 patients) and 88% (296 patients) in the CYRAMZA plus paclitaxel and placebo plus paclitaxel treatment arms, respectively

STUDY DESIGN: The phase III RAINBOW trial evaluated the efficacy and safety of CYRAMZA plus paclitaxel vs placebo plus paclitaxel in patients with locally advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- and platinum-containing chemotherapy. Major efficacy outcome measure was OS. Supportive efficacy outcome measures were PFS and ORR. All patients were ECOG PS 0 or 1. Prior to enrollment, 97% of patients had progressed during treatment or within 4 months after the last dose of first-line chemotherapy for metastatic disease. Twenty-five percent of patients had received anthracycline in combination with platinum/fluoropyrimidine therapy, while 75% did not. Patients were randomized 1:1 to CYRAMZA 8 mg/kg (n=330) or placebo (n=335) every 2 weeks (on days 1 and 15) of each 28-day cycle. Patients in both arms received paclitaxel 80 mg/m^2 on days 1, 8, and 15 of each 28-day cycle.[1,3]

*Median.

CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group performance status; GEJ=gastroesophageal junction; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

IMPORTANT SAFETY INFORMATION FOR CYRAMZA

Learn more at **CYRAMZAhcp.com**

Warnings and Precautions

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In study 1, which evaluated CYRAMZA as a single agent in advanced gastric cancer, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In study 2, which evaluated CYRAMZA plus paclitaxel, 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. 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 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.

Lilly

CYRAMZA®
ramucirumab injection
10 mg/mL solution

IMPORTANT SAFETY INFORMATION FOR CYRAMZA (CONT'D)

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%). 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. 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 who received CYRAMZA plus paclitaxel (1.2%) as compared to patients who received placebo plus paclitaxel (0.3%). 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, 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—Single Agent

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA and ≥2% higher than placebo in study 1 were hypertension (16% vs 8%; 8% vs 3%), diarrhea (14% vs 9%; 1% vs 2%), headache (9% vs 3%; 0% vs 0%), and hyponatremia (6% vs 2%; 3% vs 1%).
- The most common serious adverse events with CYRAMZA in study 1 were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients in study 1 were: neutropenia (4.7% vs 0.9%), epistaxis (4.7% vs 0.9%), rash (4.2% vs 1.7%), intestinal obstruction (2.1% vs 0%), and arterial thromboembolic events (1.7% vs 0%).
- Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and infusion-related reactions. In study 1, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria vs 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in study 1 was 0.8% and the rate of infusion-related reactions was 0.4%.

Most Common Adverse Reactions—Combination With Paclitaxel

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus paclitaxel and ≥2% higher than placebo plus paclitaxel in study 2 were fatigue/asthenia (57% vs 44%; 12% vs 6%), neutropenia (54% vs 31%; 41% vs 19%), diarrhea (32% vs 23%; 4% vs 2%), epistaxis (31% vs 7%; 0% vs 0%), hypertension (25% vs 6%; 15% vs 3%), peripheral edema (25% vs 14%; 2% vs 1%), stomatitis (20% vs 7%; 1% vs 1%), proteinuria (17% vs 6%; 1% vs 0%), thrombocytopenia (13% vs 6%; 2% vs 2%), hypoalbuminemia (11% vs 5%; 1% vs 1%), and gastrointestinal hemorrhage events (10% vs 6%; 4% vs 2%).
- The most common serious adverse events with CYRAMZA plus paclitaxel in study 2 were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients treated with CYRAMZA plus paclitaxel received granulocyte colony-stimulating factors.
- Adverse reactions resulting in discontinuation of any component of the CYRAMZA plus paclitaxel combination in 2% or more patients in study 2 were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of the CYRAMZA plus paclitaxel-treated patients in study 2 were sepsis (3.1% for CYRAMZA plus paclitaxel vs 1.8% for placebo plus paclitaxel) and gastrointestinal perforations (1.2% for CYRAMZA plus paclitaxel vs 0.3% for placebo plus paclitaxel).

Drug Interactions

- No pharmacokinetic interactions were observed between ramucirumab (CYRAMZA) and paclitaxel.

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-G HCP ISI 17SEP2015

References: 1. CYRAMZA (ramucirumab) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2017. **2.** Wilke H, Muro K, Van Cutsem E, et al; for the RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol.* 2014;15(11):1224-1235. **3.** Data on file, Eli Lilly and Company. ONC09302014b.

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. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

INDICATIONS AND USAGE

Gastric Cancer

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic, gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

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, 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

Reversible Posterior Leukoencephalopathy Syndrome (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.

Safety data are presented from two randomized, placebo controlled clinical trials in which patients received CYRAMZA: Study 1, a randomized (2:1), double-blind, clinical trial in which 351 patients received either CYRAMZA 8 mg/kg intravenously every two weeks or placebo every two weeks and Study 2, a double-blind, randomized (1:1) clinical trial in which 656 patients received paclitaxel 80 mg/m^2 on days 1, 8, and 15 of each 28-day cycle plus either CYRAMZA 8 mg/kg intravenously every two weeks or placebo every two weeks. Both trials excluded patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or greater, uncontrolled hypertension, major surgery within 28 days, or patients receiving chronic anti-platelet therapy other than once daily aspirin. Study 1 excluded patients with bilirubin ≥1.5 mg/dL and Study 2 excluded patients with bilirubin >1.5 times the upper limit of normal.

CYRAMZA Administered as a Single Agent

Among 236 patients who received CYRAMZA (safety population) in Study 1, median age was 60 years, 28% were women, 76% were White, and 16% were Asian. Patients in Study 1 received a median of 4 doses of CYRAMZA; the median duration of exposure was 8 weeks, and 32 (14% of 236) patients received CYRAMZA for at least six months.

In Study 1, the most common adverse reactions (all grades) observed in CYRAMZA-treated patients at a rate of ≥10% and ≥2% higher than placebo were hypertension and diarrhea. The most common serious adverse events with CYRAMZA were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients versus 8.7% of patients who received placebo.

Table 1: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA in Study 1

Adverse Reactions (MedDRA)[a] System Organ Class	CYRAMZA (8 mg/kg) N=236		Placebo N=115	
	All Grades (Frequency %)	Grade 3-4 (Frequency %)	All Grades (Frequency %)	Grade 3-4 (Frequency %)
Gastrointestinal Disorders				
Diarrhea	14	1	9	2
Metabolism and Nutrition Disorders				
Hyponatremia	6	3	2	1
Nervous System Disorders				
Headache	9	0	3	0
Vascular Disorders				
Hypertension	16	8	8	3

[a]MedDRA Version 15.0.

Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients in Study 1 were: neutropenia (4.7% CYRAMZA versus 0.9% placebo), epistaxis (4.7% CYRAMZA versus 0.9% placebo), rash (4.2% CYRAMZA versus 1.7% placebo), intestinal obstruction (2.1% CYRAMZA versus 0% placebo), and arterial thromboembolic events (1.7% CYRAMZA versus 0% placebo).

Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including Grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and infusion-related reactions. In Study 1, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria versus 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in Study 1 was 0.8% and the rate of infusion-related reactions was 0.4%.

CYRAMZA Administered in Combination with Paclitaxel

Among 327 patients who received CYRAMZA (safety population) in Study 2, median age was 60 years, 31% were women, 63% were White, and 33% were Asian. Patients in Study 2 received a median of 9 doses of CYRAMZA; the median duration of exposure was 18 weeks, and 93 (28% of 327) patients received CYRAMZA for at least six months.

In Study 2, the most common adverse reactions (all grades) observed in patients treated with CYRAMZA plus paclitaxel at a rate of ≥30% and ≥2% higher than placebo plus paclitaxel were fatigue, neutropenia, diarrhea, and epistaxis. The most common serious adverse events with CYRAMZA plus paclitaxel were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients treated with CYRAMZA plus paclitaxel received granulocyte colony-stimulating factors. Adverse reactions resulting in discontinuation of any component of the CYRAMZA plus paclitaxel combination in 2% or more patients in Study 2 were neutropenia (4%) and thrombocytopenia (3%).

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

Adverse Reactions (MedDRA) System Organ Class	CYRAMZA plus Paclitaxel (N=327)		Placebo plus Paclitaxel (N=329)	
	All Grades (Frequency %)	Grade ≥3 (Frequency %)	All Grades (Frequency %)	Grade ≥3 (Frequency %)
Blood and Lymphatic System Disorders				
Neutropenia	54	41	31	19
Thrombocytopenia	13	2	6	2
Gastrointestinal Disorders				
Diarrhea	32	4	23	2
Gastrointestinal hemorrhage events	10	4	6	2
Stomatitis	20	1	7	1
General Disorders and Administration Site Disorders				
Fatigue/Asthenia	57	12	44	6
Peripheral edema	25	2	14	1
Metabolism and Nutrition Disorders				
Hypoalbuminemia	11	1	5	1
Renal and Urinary Disorders				
Proteinuria	17	1	6	0
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	31	0	7	0
Vascular Disorder				
Hypertension	25	15	6	3

Clinically relevant adverse reactions reported in ≥1% and <5% of the CYRAMZA plus paclitaxel treated patients in Study 2 were sepsis (3.1% CYRAMZA plus paclitaxel versus 1.8% placebo plus paclitaxel) and gastrointestinal perforations (1.2% CYRAMZA plus paclitaxel versus 0.3% for placebo plus paclitaxel).

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 interactions were observed between ramucirumab and paclitaxel.

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.

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.

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 either as a single agent or in combination with weekly paclitaxel is 8 mg/kg every 2 weeks administered as an intravenous infusion over 60 minutes. Continue CYRAMZA until disease progression or unacceptable toxicity. When given in combination, administer CYRAMZA prior to administration of paclitaxel.

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-related 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 6 mg/kg every 2 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 5 mg/kg every 2 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 paclitaxel, refer to the current 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.

Eli Lilly and Company, Indianapolis, IN 46285, USA

RB-G HCP BS 27MAR2017

PP-RB-US-0985

COMMUNITY PHARMACY

PBMs: Their Role, the Problems, and How Practices Can Work With Them

Ray Bailey, RPh, and Ricky Newton, CPA

COPA COMMUNITY ONCOLOGY PHARMACY ASSOCIATION

continued from cover

Adverse reactions and dosing refinements are common in oncology care and require prompt attention by someone familiar with patient history. PBMs do not have access to patient medical records and are, therefore, hampered in their ability to understand and resolve problems. In contrast, community oncology pharmacists and pharmacy technicians, working under the supervision of their community oncologists, have access to patient medical records and are familiar with the 50-plus oral anticancer agents, the most frequent and expected reactions, and the most prompt and effective response.

Community oncology-based pharmacists, pharmacy technicians, and oncologists know their patients and the drugs in ways PBMs do not. PBMs are very much on board with dispensing many drugs, but they may have less experience with the more varied and critical care cancer drugs. PBMs are well-suited to manage the orals process, to adjudicate claims, and to manage the process of obtaining drugs, but they are not experts in determining drug access options.

The Role of the Community Oncology Pharmacist and Pharmacy Technicians

During traditional chemotherapy, patients are very closely monitored by clinic staff—from the lab technicians, pharmacists, pharmacy technicians, nurses, nurse practitioners, and chemotherapy nurses to the physicians. This changes with oral drugs, placing a much greater responsibility on the pharmacist and pharmacy technicians.

In most practices, it is the responsibility of the dispensing pharmacist, lab technician, and oncologist to manage the patients receiving oral chemotherapy. These chemotherapy agents often carry the same risks and reactions as an intravenous chemotherapy agent. In the absence of a linear connection between dispensing and patient management, there is a disconnect that affects treatment, compliance, outcomes, and the cost of care for patients.

It is not only the standard of care, but also required by law in most states, that the dispensing pharmacist, pharmacy technicians, and oncologists are responsible for patient education and management. For oral cancer drugs, this includes dosing plan explanation (eg, should the drug be taken with or without food, drug storage and handling, possible adverse reactions, how to mitigate those reactions, monitoring compliance, and when to provide medical intervention). Based on their knowledge of the agents, community oncology pharmacists and pharmacy technicians are prepared make recommendations to the oncologist for OTC medications or supportive care medications that can ameliorate common reactions, such as diarrhea or skin toxicities, rather than discontinuing treatment. They are familiar with options such as dosing changes and/or drug holidays, and they recognize signs of toxicity and know when lab testing, in-office hydration, or other supportive care may be warranted. Recognition of these signs can avoid disruptive occurrences, such as trips to the emergency department.

Community oncology-based pharmacists, pharmacy technicians, and oncologists have access to patient records and can more closely monitor patients which empowers them to provide the most coordinated care. These tools are not available to anyone outside the practice, including PBMs.

The Most Common Problems

Delays

Patients receiving their oral drugs from a community oncology practice have access to those drugs within 24 hours of prescribing, and they begin treatment immediately. Patients receiving their oral cancer drugs through a PBM, on the other hand, often have a much longer wait, sometimes 14 days or more. Common causes of delays include:

- More complicated or cumbersome internal PBM protocols that require more time to process a prescription
- Multiple back-and-forth conversations between the PBM and the practice
- Time needed to confirm and re-confirm patient information, including addresses and insurance coverage, as well as additional information requests
- Transferring prescriptions for processing between facilities for actual dispensing
- Mail delivery time
- Insurance verification and approval
- Providing patient financial assistance

Poaching

Some PBMs force patients currently receiving their oral drugs from the community oncologist to switch to pharmacies that the PBM owns. However, PBMs are often disconnected from the patients and may invoke internal systems that make presumptions about the preferred method of care and attempt to dispense drugs without evaluating what might be the best care, from the patient's perspective.

For drug prior authorization, PBMs document all of the information necessary for subsequent prescriptions, including the physician and patient names, payer information, drug name, dosage, and authorization. Some PBMs will automatically create a prescription and fax it to the physician. Without scrutiny from the oncologist or staff, patients may be directed away from the practice's pharmacy.

Trolling and Steering

Physician dispensing has become increasingly popular in the United States and has expanded to include a variety of medications in both the retail and specialty spaces. This growth in popularity has largely benefited overall patient care. William Shell, MD, in *The History of Physician Dispensing*, reports that patient compliance with drug therapy is 60% to 70% higher from a dispensing physician than a pharmacy.[1] »

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Patients cannot be compelled to fill their prescription from a specific dispenser; however, many report receiving correspondence from their PBM that implies they must use a pharmacy owned by the PBM. These letters often explain that the insurance company has its own pharmacy, from which the patient may already be receiving other prescribed drugs, and offer for the patient to also get their oral cancer drug from this same source. Many patients find this confusing and do not understand the repercussions that jeopardize the monitoring, care control, and care management that they receive at their community oncology pharmacy, and they mistakenly, or unintentionally, switch their drug dispenser.

A community oncology pharmacist will recognize drugs that may be difficult to tolerate or patients whose conditions may require multiple dosing refinements. In these cases, in anticipation of modifications, practices will often dispense a 15-day supply rather than a 30- or 90-day supply. PBMs can lack the expertise for such forethought or do not have the experience with care management to know when a smaller supply might be the wiser, more economical choice. In-house pharmacies are often able to lower medication waste in cases when a patient's drug dose is expected to be reduced or when drug tolerance is a consideration.

Caring for Patients, Coping With PBMs

Although PBM problems are not guaranteed, patient care is enhanced when a practice is aware of what may happen and is prepared to handle problems as soon as they arise. Practices that have coping systems in place and have developed ways of dealing with the PBM problems can enhance patient care and avoid treatment delays.

Pick Up the Phone

PBMs may delay shipping a drug because they require address confirmation; they often send a letter requesting address confirmation to the very address they wish to confirm. Other times patients wait, often too patiently, for overdue drugs. Paper work problems, red tape, and conflicting or missing information are often easily resolved with a short conversation. Relatively simple problems that can cause unnecessary delays can usually be resolved just by picking up the phone.

Community Oncology Pharmacy Association Support

The Community Oncology Pharmacy Association (COPA), within the Community Oncology Alliance (COA), was formed in response to the increasing number of community cancer clinics dispensing oral cancer drugs and ancillary therapies. COPA is a nonprofit entity that has established standards; provides information, education, and resources; enhances information exchange; and advocates for the patient-centric model of integrated, high-quality cancer care. Due to the increasing costs of cancer drugs, there are commercial interests, such as PBMs and specialty pharmacies, attempting to separate oral cancer therapy from the point-of-care and oncologist control, thus interfering with the physician-patient relationship. As a nonprofit focused on enhancing patient care, COPA is in the unique position of serving as a noncommercial organization dedicated to addressing a variety of pharmacy-related issues, all in the sole interest of patient care.

Community oncology practices need to work with pharmacists to ensure patients have their prescribed drugs.

COPA provides tools that can assist practices in resolving issues with PBMs and benefit patients, including:

- Letter templates when challenging, usually in cases of steering, PBM violation of the Health Insurance Portability and Accountability Act and other laws
- Access to State Boards of Pharmacy consumer complaint forms to report incidents of interference in the physician-patient relationship over drug dispensing
- Access to HHS' Office for Civil Rights (OCR) forms to file a Health Information Privacy Complaint

Internal Practice Systems

Many larger practices are developing internal protocols to deal with some of the most common problems. Rapid referral systems establish procedures for follow-up—daily, when necessary—if a delay of the onset of treatment due to drug delays could be detrimental to the patient's prognosis. Follow-up systems enable practices to track prescriptions as they move through a PBM system, avoiding potential delays and preventing intentional or unintentional poaching, trolling, or steering.

Incident Report Collection

COPA has also developed a system to document incidents of PBM abuses by collecting data on PBM and specialty pharmacy-related incidents to identify trends, patient care issues, and pricing issues and to provide tools that can ensure maximum patient benefit. These data are also available to support proposed regulatory or legislative action. COPA also maintains a chronology of actual patient stories of PBM abuses. Go to **coapharmacy.com** to review the complete listing in Real Life Impact of Pharmacy Benefit Managers: April 2017, May 2017, September 2017.

Next Steps

Community oncologists expect their pharmacists to make sure patients have their prescribed drugs—whether from the practice or a PBM—and are fully educated and compliant and properly monitored and managed. PBMs can be both part of the problem and the solution to meeting those expectations. When they are part of the problem, community oncology pharmacists and pharmacy technicians are not alone and have tools to help them help patients. ◆

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Additional information about PBMs and their impact on community oncology practices can be found here: **onclive.com/link/1485**.

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Positive Quality Interventions: An Innovative Platform for Oncology Practice Collaboration

Joshua Nubla, PharmD; Neal Dave, PharmD; and Michael Reff, RPh, MBA

continued from cover

NUBLA

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with consistent and updated education material that succinctly describes and explains the primary details of treatment with specific medications, including but not limited to compliance obstacles and solutions, instructions on managing side effects and major adverse effects, and expectations of therapeutic onset and duration.

To this effect, the National Community Oncology Dispensing Association, Inc (NCODA), has developed education material dedicated to the promotion of better patient care in the oncology setting. Called Positive Quality Intervention (PQI), the material is developed by NCODA members across oncology practices throughout the United States who share their best practices. With numerous therapies to cover, a healthcare team must efficiently manage and allocate resources, a task that can potentially lead to competing priorities. A patient's attention must also be directed toward other facets of dispensing, such as financial assistance and healthcare navigation. Sharing information across the organization can help clinicians stay current and help drive positive patient care interactions. An eye on the overall health of a patient and the ability to provide affordable healthcare and patient satisfaction can push the practice of oncology pharmacy forward.[1]

Background

In the 2000s, approximately 20% of the cancer medications in use were oral therapies. That number has nearly doubled, with oral medications making up 40% of treatments now used in oncology, in tandem with diagnostic and surgical procedures as well as various pharmacy-driven regimens that continue to expand every day.[2] Barriers to effective use of oral anticancer agents include low adherence and patient literacy. Patients are often confused with the vast amount of information they receive, right from diagnosis and initiation of treatment, and some may also be intimidated by the regimen itself. Miscommunication of therapy regimens can lead to lower adherence and reduced treatment efficacy, increased hospitalization, disease progression, and increased health costs for both the patient and the provider network.

Trying to stay up-to-date on targeted oral medications that are indicated for only certain types of rare cancer can be challenging. Each new oral agent has its own specific barriers that could lead to patients' not being able to successfully stay on therapy long enough or not being able to benefit fully.

Education Efforts by NCODA

NCODA's PQI is designed with both the pharmacist and patient in mind. The treatment and management of oncology patients on oral drug therapy is constantly evolving. The professionals at in-office dispensing practices are uniquely positioned to ensure appropriate treatment, increase compliance, and maximize patient health outcomes. As NCODA quality standards, PQIs are designed to operationalize and standardize those practices to achieve these positive clinical outcomes. NCODA's quality standards, publicly available on the organization's website,[3] are built into 4 domains that work cohesively with one another to create a more standardized and effective form of oncology practice[3]:

1) Patient centered
2) Positive quality interventions
3) Foundational elements
4) Health information technology (IT)

The 4 quality standards of NCODA help drive the basis of PQI while simultaneously being influenced by the PQIs themselves. The primary components of these standards can yield improved management of oral oncolytics in patient care:

1. Patient centered

With the objective of providing exceptional patient care, in-office dispensing practices should focus on maximizing patient convenience, providing timely access to treatment, ensuring financial support, and delivering individualized patient education. Developing a strong relationship with the patient is extremely important for sustaining and growing a practice toward better patient care. This involves, but is not limited to, direct access to patients and reviewing patient therapy regimens through direct patient interaction, developing standards of practice for dispensing the medication to the patient, and monitoring overall patient safety. Consistent patient vigilance with ever-changing regimens and therapy transitions is necessary to avoid medication waste and extraneous expenses. Cost avoidance is key to any clinical practice, and by adequate resource management, practices can obtain more effective value from treatment regimens. A strong patient-centered focus can increase patient compliance and adherence to medication and result in a more persistent regimen that can have a stronger overall therapeutic response.[3]

2. PQIs

PQIs were developed to ensure that a patient-centric model exists at all times within the in-office dispensing setting and to improve the overall management of patients who receive oral cancer medications. Interventions made by NCODA members and professionals were created, reviewed, and implemented to increase the speed to therapy, reduce costs and hospitalizations, improve persistence and compliance, and provide a higher level of patient care.

By identifying and recommending appropriate therapy, practices face inherent challenges in keeping current with new drug approvals, new indications, and compendia/guideline updates:

- Helping to minimize and manage the toxicities associated with treatment, with the goal of keeping patients on consistent therapy as long as efficaciously possible
- Providing an efficient operation of a demanding dispensing process
- Designing medication management tools that focus on specific issues associated with managing oral drug therapies for cancer

Using the practice of evidence-based medicine, the PQIs are developed for specific medications and/or diseases and continuously guide in-office dispensing professionals in managing

a patient's drug therapy. Through PQIs, practices are able to mitigate toxicities and assist providers by highlighting appropriate drug therapy and dose based on individual patient characteristics.[3]

PQIs involve clinical reference tools to establish an up-to-date library of education for all practices involved in oral medications for oncology. The education materials themselves, which are reviewed by NCODA professionals and archived, can be accessed and used by practices for patients at an acceptable literacy level for effective communication during the counseling phase of dispensing. These materials will be made available online as well as through monthly meetings for healthcare professionals through NCODA, providing both literary and audio support. The material also includes standards of practice for inventory maintenance for timely initiation as well as assistance in pharmacist verification and validation.

3. Foundational elements

Foundational elements are established to facilitate the ongoing nature of pharmacy operational elements, which include:

- Workflow and process flow diagrams, including both single- and multisite practices and dispensing areas
- Central business office alignment, which refers to the integration of billing services and billing reconciliation
- Contracting and payer implementation
- Prior authorization processing
- Group purchasing organization affiliations
- Liability insurance
- Claims accounting, which involves editing, adjudication, and reconciliation
- Audit preparation and readiness
- Credit card processing companies
- Cost-avoidance documentation
- Financial counseling and patient advocacy

This quality standard interfaces with creating a proper dispensing space; a thorough communication plan involving healthcare providers, patients, and auxiliary staff; continuous quality improvement; and corrective/preventive action assessments for standards of procedure to fulfill an all-encompassing healthcare process.[3]

4. Health IT

Having data integrated into oncology dispensing pharmacy platforms is critical to closing the gaps in educational material and improving on the patient-centered model. The ability to closely link to prescriber-level data provides a distinct advantage in helping to manage patients and track multiple data points such as adverse drug reactions, dose changes, cost avoidance, medication waste, and therapy discontinuation. Being able to provide additional care beyond the first medication fill is crucial to creating a stronger connection to the patient and data points such as financial support and adherence rate. One of the most underused aspects of community oncology care is the vast amount of contact time with the patient involving both subjective and objective data. Tapping consistent data provides the ability to predict future trends in therapy education and management, for which NCODA can create proactive education to manage an ever-changing oncology landscape. Broadening those trends over the large network of NCODA member practices across the country can exponentially increase the speed and brevity at which best practices can be developed to suit the needs of the healthcare provider community.[3]

Future Data Collection

NCODA is collaborating with promising health IT initiatives that will better interface with pharmacy dispensing systems to help evaluate the impact of the PQIs. Areas of interest include evaluating how long patients stayed on therapy and whether emergency department visits and hospitalizations were reduced when information written in a PQI was followed. This type of analysis will be vital in the new quality-driven positive-outcomes world. The data would be gathered across large and small NCODA practices as well as those that have or have not participated in the Oncology Care Model (OCM). Documenting a positive impact with PQIs will confirm the quality care that patients receive at oncology centers and also lend support to the in-office dispensing model.

The prospective outlook on the oral oncology space will be evaluated with future PQIs. Quantitative measurement of these early initiatives, however, may require a different outlook. We can possibly evaluate NCODA members, in both OCM and non-OCM practices, who perform best practice surveys before implementation of PQIs at a predetermined time range—for example 6 months prior to and then 2 months after PQI implementation. A comparison of practice changes can provide preliminary evidence about the impact of PQIs as well as the depth of oncology practice overall.

Current PQIs

The PQI pipeline developed by NCODA is dictated by the reported needs of NCODA members and includes broad topics such as medication-related adverse event management. With the addition of practices in various degrees of size and scope, the network of information developed will help create standardized resources for a growing range of healthcare systems. The sharing of best practices facilitates the evolution and improvement of oncology care across the healthcare setting.[3]

NCODA's constantly growing list of PQIs has been addressing the following topics:

- Hand-foot syndrome
- Stomatitis
- Chemotherapy-induced diarrhea
- Metastatic colorectal cancer (mCRC)
- Epidermal growth factor receptor medications
- Polycythemia vera
- Myelofibrosis
- mCRC (trifluridine and tipiracil)
  - Dose reduction practices
- Specific drug-based follow-up call schedule
- Olanzapine use for nausea prevention
- Hepatocellular carcinoma
- Cyclin-dependent kinase 4 inhibitors

Conclusion

Advancing the value of dispensing practices for oncology physicians constitutes a significant part of the NCODA mission. The need for best dispensing practices in the oncology setting is increasingly becoming apparent, and PQIs play an integral role in helping achieve this. With the PQI initiative, NCODA members across cancer centers can use their collaborative power to develop best practices that can lead to the best possible patient care.

Pharmacists, nurses, pharmacy technicians, and physicians make up the diverse group of NCODA's membership. Each professional contributes and helps make the organization and its mission possible and successful. By creating a new type of progressive practice network focused on standardizing the oncology field, NCODA is able to prepare for the incoming wave of oral oncology medications that cover more tailored therapy regimens across a wide pool of varying patient demographics. Positive quality interventions are designed to fulfill the triple aim of improving patient satisfaction and care quality, improving the health of the overall population, and reducing the per capita cost of healthcare.[1] With future data-collection methods and a pipeline of PQI creation in place, these standardized practices will help extend patient therapy and prevent loss of efficacy which will lead to better care throughout the comprehensive oncology space. ◆

FUNDING SOURCE: N/A

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Creating connections.
Inspired by patients.

Commitment to patients and innovation fueled the advancement of the Celgene portfolio from hematology and oncology into inflammatory diseases. Those same principles guide our approach to making sure patients can get the essential treatments they need.

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