SPECIAL ISSUE: ALTERNATIVE PAYMENT MODELS

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Evidence-Based ONCOLOGY™

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ALSO IN THIS ISSUE

AN OVERVIEW OF PAYMENT MODELS IN ONCOLOGY

What are alternative payment models (APMs) and how are clinics and institutions developing these? What drives the success of APMs in oncology care? Harold D. Miller of the Center for Healthcare Quality and Payment Reform (SP160) and Sachin M. Apte, MD, MS, MBA, of the Moffitt Cancer Center (SP169) help answer some of these questions.

DISCREPANCIES IN MEDICARE PAYMENT FOR BONE MARROW TRANSPLANTS

Jeffrey W. Chell, MD, CEO of the National Bone Marrow Donor Program, brings forth issues with federal payment policies that can prevent access to life-saving bone marrow transplants for patients enrolled in Medicare. These discrepancies are a product of different reimbursement rules for inpatient versus outpatient transplant procedures (SP173).

IN-HOUSE PHARMACY SUCCESS

The decision to expand in-house pharmacy operations to include specialty pharmacy, especially oncology agents, created cost savings and better care for patients at the Smilow Cancer Hospital at Yale-New Haven. Kerin Adelson, MD, is the lead author of the Smilow study, presented at the American Society of Clinical Oncology's Quality Care Symposium (SP187).

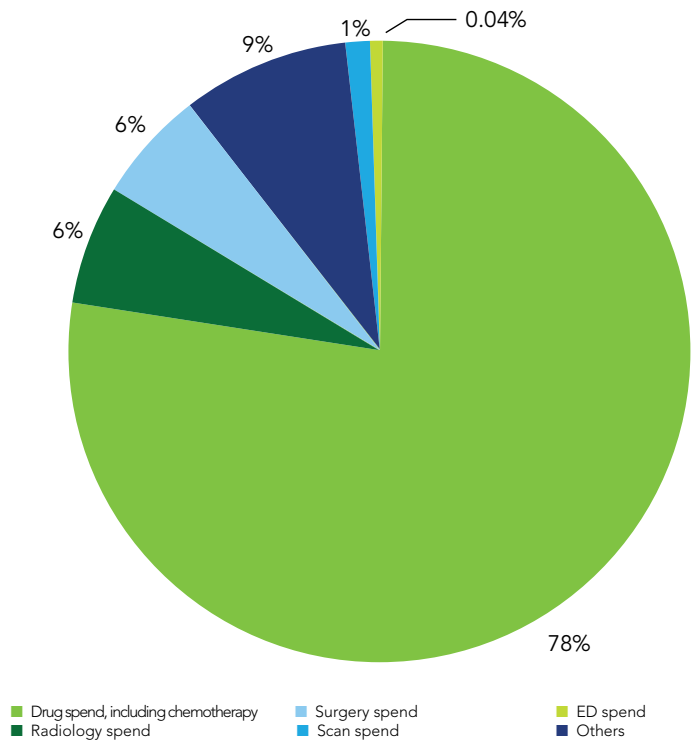
VALUE-BASED MODELS

Value-based Payment Models in Oncology: Will They Help or Hinder Patient Access to New Treatments?

Sonal Shah, PharmD, and Greg Reh

INTRODUCTION

The costs of treating cancer are rising—approximately $124.6 billion in 2010 in the United States and projected to grow to $158 billion to $173 billion by 2020.[1] Increased spending on cancer care can be attributed to a number of factors, including an aging population, growth in the number of individuals with insurance coverage, earlier diagnoses, and longer survival rates. We have also made advances in surgeries, radiation therapies, and medications—including advanced immunotherapies and targeted therapeutics. But these advancements are paralleled with rising treatment costs.



Today, many health plans, health systems, and oncology groups have begun experimenting with value-based payment models to control rising costs, reduce unexplained variation in care, and improve patient outcomes. Four value-based payment models are being tested in the commercial market:

1. Financial incentives for adhering to clinical pathways
2. Patient-centered medical homes (PCMHs)
3. Bundled payments
4. Specialty accountable care organizations (ACOs).

CONTINUED ON SP188

HEALTH IT

Why Oncologists Need Technology to Succeed in Alternative Payment Models

Brenton Fargnoli, MD; Ryan Holleran; and Michael Kolodziej, MD

WITH THE LAUNCH OF MEDICARE'S Oncology Care Model (OCM), and commercial insurers' initiation of value-based payment pilots, there has been much discussion around model design, care delivery reform, financial impact (including the cost of transformation), and quality of care. Notably absent from much of this discussion are practical aspects of how practices will do the work. As such, the operational lift for practices has not been given the detailed consideration it deserves as these models have been developed.

Practices face 3 major challenges in today's value-based payment models:

1. Administrative needs, including patient identification and tracking, technical performance and documentation of care plan completion, and quality metric calculation and reporting
2. Identification of old care processes that require transformation, and implementation of new ones
3. Using analytics to measure practice performance on both financial and clinical measures, with the overall goal of improved quality of care at lower cost

CONTINUED ON SP196

PHYSICIAN PERSPECTIVE

Making Sense of Advanced Payment Models

Barbara McAneny, MD; Stephen S. Grubbs, MD; Walter Birch, MBA; Dan Sayam Zuckerman, MD

THE REPEAL OF THE Sustainable Growth Rate and its replacement with the Medicare Access and CHIP [Children's Health Insurance Program] Reauthorization Act of 2015 (MACRA) authorized CMS to establish the new Quality Payment Program (QPP) to promote the transition of medical payments from volume to value. The QPP reimburses Part B medical services through one of 2 methodologies:

- The first track reimburses through the Merit-based Incentive Payment System (MIPS)

CONTINUED ON SP199

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The only CDK4/6 inhibitor approved based on a first-line, phase III study that met its primary end point early

NEW

KISQALI®

ribociclib

Indication

KISQALI® (ribociclib) is indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

Important Safety Information

QT interval prolongation. KISQALI has been shown to prolong the QT interval in a concentration-dependent manner, with estimated mean increase in QTc interval exceeding 20 ms (22.9 ms [90% CI: 21.6-24.1]) at the mean steady-state C_{max} following administration at the 600-mg once-daily dose. In MONALEESA-2, one patient (0.3%) had >500 msec postbaseline QTcF value (average of triplicate), and 9 of 329 patients (3.0%) had a >60 msec increase from baseline in QTcF intervals (average of triplicate). These electrocardiogram (ECG) changes occurred within the first 4 weeks of treatment and were reversible with dose interruption. There were no reported cases of Torsades de Pointes. Syncope occurred in 9 patients (2.7%) in the KISQALI + letrozole arm vs 3 patients (0.9%) in the placebo + letrozole arm. In the KISQALI + letrozole treatment arm, there was 1 (0.3%) sudden death in a patient with grade 3 hypokalemia and grade 2 QT prolongation.

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values <450 msec. Repeat ECG at approximately day 14 of the first cycle, at the beginning of the second cycle, and as clinically indicated. Monitor serum electrolytes (including potassium, calcium, phosphorus, and magnesium) prior to the initiation of treatment, at the beginning of each of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting therapy with KISQALI.

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QTc prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
- electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong the QTc interval and/or strong CYP3A inhibitors, as this may lead to prolongation of the QTcF interval. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction, or discontinuation.

Hepatobiliary toxicity. In MONALEESA-2, increases in transaminases were observed. Grade 3 or 4 increases in alanine aminotransferase (ALT) (10% vs 1%) and aspartate aminotransferase (AST) (7% vs 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had grade ≥3 ALT/AST elevation, the median time to onset was 57 days for the KISQALI + letrozole treatment group. The median time to resolution to grade ≤2 was 24 days in the KISQALI + letrozole treatment group.

Concurrent elevations in ALT or AST >3 times the upper limit of normal (ULN) and total bilirubin >2 times the ULN, with normal alkaline

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phosphatase, in the absence of cholestasis occurred in 4 patients (1%) in MONALEESA-2, and all patients recovered after discontinuation of KISQALI.

Perform liver function tests (LFTs) before initiating therapy with KISQALI. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation. Recommendations for patients who have elevated AST/ALT grade ≥3 at baseline have not been established.

Neutropenia. In MONALEESA-2, neutropenia was the most frequently reported adverse reaction (AR) (75%), and a grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 60% of patients receiving KISQALI + letrozole. Among the patients who had grade 2, 3, or 4 neutropenia, the median time to grade ≥2 was 16 days. The median time to resolution of grade ≥3 (to normalization or grade <3) was 15 days in the KISQALI + letrozole treatment group. Febrile neutropenia was reported in 1.5% of patients receiving KISQALI and letrozole. Treatment discontinuation due to neutropenia was 0.9%.

Perform complete blood count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction, or discontinuation.

Embryo-fetal toxicity. Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of KISQALI to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve. Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose.

Adverse reactions. The most common ARs reported in the KISQALI + letrozole arm (frequency ≥20%) were neutropenia (75%), nausea (52%), fatigue (37%), diarrhea (35%), leukopenia (33%), alopecia (33%), vomiting (29%), constipation (25%), headache (22%), and back pain (20%). The most common grade 3/4 ARs (reported at a frequency >2%) were neutropenia (60%), leukopenia (21%), abnormal LFTs (10%), lymphopenia (7%), and vomiting (4%).

Laboratory abnormalities. The most common laboratory abnormalities occurring in patients receiving KISQALI + letrozole (all grades, incidence ≥20%) were leukocyte count decrease (93%), neutrophil count decrease (93%), hemoglobin decrease (57%), lymphocyte count decrease (51%), ALT increase (46%), AST increase (44%), platelet count decrease (29%), and creatinine increase (20%). The most common grade 3/4 laboratory abnormalities (incidence >2%) were neutrophil count decrease (60%), leukocyte count decrease (34%), lymphocyte count decrease (14%), ALT increase (10%), AST increase (7%), and phosphorus decrease (6%).

AI=aromatase inhibitor; CDK=cyclin-dependent kinase; FDA=U.S. Food and Drug Administration.

For more information, contact your local Novartis representative or visit KISQALI.com.

Please see Brief Summary of Prescribing Information on adjacent pages.

KISQALI® ribociclib

KISQALI® (ribociclib) tablets, for oral use
Initial U.S. Approval: 2017

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

KISQALI® is indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 QT Interval Prolongation

KISQALI has been shown to prolong the QT interval in a concentration-dependent manner, with estimated mean increase in QTc interval exceeding 20 ms (22.9 ms (90% CI: 21.6, 24.1)) at the mean steady-state C_{max} following administration at 600 mg once daily dose *[see Clinical Pharmacology (12.2) in the full prescribing information]*. In Study 1 (MONALEESA-2), one patient (0.3%) had >500 msec post-baseline QTcF value (average of triplicate), and nine patients out of 329 patients (3%) had a >60 msec increase from baseline in QTcF intervals (average of triplicate). These ECG changes occurred within the first four weeks of treatment and were reversible with dose interruption. There were no reported cases of Torsades de Pointes. Syncope occurred in 9 patients (2.7%) in the KISQALI plus letrozole arm versus 3 (0.9%) in placebo plus letrozole arm. On the KISQALI plus letrozole treatment arm, there was one (0.3%) sudden death in a patient with Grade 3 hypokalemia and Grade 2 QT prolongation *[see Adverse Reactions (6)]*.

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values less than 450 msec. Repeat ECG at approximately Day 14 of the first cycle and the beginning of the second cycle, and as clinically indicated.

Monitor serum electrolytes (including potassium, calcium, phosphorous and magnesium) prior to the initiation of treatment, at the beginning of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting KISQALI therapy *[see Dosage and Administration (2.2) in the full prescribing information]*.

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QTc prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmias
- electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong QTc interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction or discontinuation as described in Table 4 *[see Dosage and Administration (2.2) in the full prescribing information and Drug Interactions (7.4)]*.

5.2 Hepatobiliary Toxicity

In Study 1, increases in transaminases were observed. Grade 3 or 4 increases in ALT (10% versus 1%) and AST (7% versus 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had Grade ≥ 3 ALT/AST elevation, the median time-to-onset was 57 days for the KISQALI plus letrozole treatment group. The median time to resolution to Grade ≤ 2 was 24 days in the KISQALI plus letrozole treatment group.

Concurrent elevations in ALT or AST greater than three times the ULN and total bilirubin greater than two times the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 4 (1%) patients in Study 1 and all patients recovered after discontinuation of KISQALI.

Perform LFTs before initiating therapy with KISQALI. Monitor LFTs every 2 weeks for first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated *[see Dosage and Administration (2.2) in the full prescribing information]*.

Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation as described in Table 3 (Dose Modification and Management for Hepatobiliary Toxicity) *[see Dosage and Administration (2.2) in the full prescribing information]*. Recommendations for patients who have elevated AST/ALT Grade ≥ 3 at baseline have not been established.

5.3 Neutropenia

In Study 1, neutropenia was the most frequently reported adverse reaction (75%) and a Grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 60% of patients receiving KISQALI plus letrozole. Among the patients who had Grade 2, 3, or 4 neutropenia, the median time to Grade ≥ 2 neutropenia was 16 days. The median time to resolution of Grade ≥ 3 (to normalization or Grade < 3) was 15 days in the KISQALI plus letrozole treatment group. Febrile neutropenia was reported in 1.5% of patients receiving KISQALI and letrozole. Treatment discontinuation due to neutropenia was 0.9%.

Perform CBC before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.

Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction or discontinuation as described in Table 2 *[see Dosage and Administration (2.2) in the full prescribing information]*.

5.4 Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ribociclib to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve (AUC). Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose *[see Use in Specific Population (8.1, 8.3) and Clinical Pharmacology (12.1) in the full prescribing information]*.

6 ADVERSE REACTIONS

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

- QT Interval Prolongation *[see Warnings and Precautions (5.1)]*
- Hepatobiliary Toxicity *[see Warnings and Precautions (5.2)]*
- Neutropenia *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trial Experience

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

The safety data reported below are based on Study 1 (MONALEESA-2), a clinical study of 668 postmenopausal women receiving KISQALI plus letrozole or placebo plus letrozole. The median duration of exposure to KISQALI plus letrozole was 13 months with 58% of patients exposed for ≥ 12 months.

Dose reductions due to adverse reactions (ARs) occurred in 45% of patients receiving KISQALI plus letrozole and in 3% of patients receiving placebo plus letrozole. Permanent discontinuations due to ARs were reported in 7% of patients receiving KISQALI plus letrozole and 2% in patients receiving placebo plus letrozole. The most common ARs leading to treatment discontinuation of KISQALI in patients receiving KISQALI plus letrozole were ALT increased (4%), AST increased (3%), vomiting (2%). Antiemetics and antidiarrhea medications were used to manage symptoms as clinically indicated.

On-treatment deaths, regardless of causality, were reported in three cases (0.9%) of KISQALI plus letrozole treated patients vs. one case (0.3%) of placebo plus letrozole treated patients. Causes of death on KISQALI plus letrozole included one case each of the following: progressive disease, death (cause unknown), and sudden death (in the setting of Grade 3 hypokalemia and Grade 2 QT prolongation).

The most common ARs (reported at a frequency ≥ 20%) were neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache and back pain.

The most common Grade 3/4 ARs (reported at a frequency > 2%) were neutropenia, leukopenia, abnormal liver function tests, lymphopenia, and vomiting.

ARs and laboratory abnormalities occurring in patients in Study 1 are listed in Table 6 and Table 7, respectively.

Table 6: Adverse Reactions Occurring in ≥ 10% and ≥ 2% higher than Placebo Arm in Study 1 (All Grades)

	KISQALI + letrozole N=334			Placebo + letrozole N=330		
Adverse drug reactions	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Infections and Infestations						
Urinary tract infection	11	1	0	8	0	0
Blood and lymphatic system disorders						
Neutropenia	75	50	10	5	1	0
Leukopenia	33	20	1	1	<1	0
Anemia	18	1	<1	5	1	0
Lymphopenia	11	6	1	2	1	0
Metabolism and nutrition disorders						
Decreased appetite	19	2	0	15	<1	0
Nervous system disorders						
Headache	22	<1	0	19	<1	0
Insomnia	12	<1	0	9	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea	12	1	0	9	1	0
Musculoskeletal and connective tissue disorders						
Back pain	20	2	0	18	<1	0
Gastrointestinal disorders						
Nausea	52	2	0	29	1	0
Diarrhea	35	1	0	22	1	0
Vomiting	29	4	0	16	1	0
Constipation	25	1	0	19	0	0
Stomatitis	12	<1	0	7	0	0
Abdominal pain	11	1	0	8	0	0
Skin and subcutaneous tissue disorders						
Alopecia	33	0	0	16	0	0
Rash	17	1	0	8	0	0
Pruritus	14	1	0	6	0	0
General disorders and administration site conditions						
Fatigue	37	2	<1	30	1	0
Pyrexia	13	<1	0	6	0	0
Edema peripheral	12	0	0	10	0	0
Investigations						
Abnormal liver function tests[1]	18	8	2	6	2	0

Grading according to CTCAE 4.03 (Common Terminology Criteria for Adverse Events)
[1]abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased

Table 7: Laboratory Abnormalities Occurring in ≥ 10% of Patients in Study 1

	KISQALI + letrozole N=334			Placebo + letrozole N=330		
Laboratory parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
HEMATOLOGY						
Leukocyte count decreased	93	31	3	29	1	< 1
Neutrophil count decreased	93	49	11	24	1	< 1
Hemoglobin decreased	57	2	0	26	1	0
Lymphocyte count decreased	51	12	2	22	3	1
Platelet count decreased	29	1	< 1	6	0	< 1
CHEMISTRY						
Alanine aminotransferase increased	46	8	2	36	1	0
Aspartate aminotransferase increased	44	6	1	32	2	0
Creatinine increased	20	1	0	6	0	0
Phosphorous decreased	13	5	1	4	1	0
Potassium decreased	11	1	1	7	1	0

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Ribociclib Plasma Concentrations

CYP3A4 Inhibitors

Coadministration of a strong CYP3A4 inhibitor (ritonavir) increased ribociclib exposure in healthy subjects by 3.2-fold *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Avoid concomitant use of strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, and voriconazole) and consider alternative concomitant medications with less potential for CYP3A inhibition.

If coadministration of KISQALI with a strong CYP3A inhibitor cannot be avoided, reduce the dose of KISQALI to 400 mg once daily *[see Dosage and Administration (2.2) in the full prescribing information]*.

Instruct patients to avoid pomegranates or pomegranate juice, grapefruit, all of which are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to ribociclib *[see Patient Counseling Information (17) in the full prescribing information]*.

7.2 Drugs That May Decrease Ribociclib Plasma Concentrations

CYP3A4 Inducers

Coadministration of a strong CYP3A4 inducer (rifampin) decreased the plasma exposure of ribociclib in healthy subjects by 89% *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Avoid concomitant use of strong CYP3A inducers and consider an alternate concomitant medication with no or minimal potential to induce CYP3A (e.g., phenytoin, rifampin, carbamazepine and St John's Wort (Hypericum perforatum)).

7.3 Effect of KISQALI on Other Drugs

CYP3A substrates with narrow therapeutic index

Coadministration of midazolam (a sensitive CYP3A4 substrate) with multiple doses of KISQALI (400 mg) increased the midazolam exposure by 3.8-fold in healthy subjects, compared with administration of midazolam alone *[see Clinical Pharmacology (12.3) in the full prescribing information]*. KISQALI given at the clinically relevant dose of 600 mg is predicted to increase the midazolam AUC by 5.2-fold. Therefore, caution is recommended when KISQALI is administered with CYP3A substrates with a narrow therapeutic index. The dose of a sensitive CYP3A substrate with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus, may need to be reduced as ribociclib can increase their exposure.

7.4 Drugs That Prolong the QT Interval

Avoid coadministration of KISQALI with medicinal products with a known potential to prolong QT such as antiarrhythmic medicines (including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol), and other drugs that are known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and ondansetron (i.v)) *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3) in the full prescribing information]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) in the full prescribing information]*.

There are no available human data informing the drug-associated risk. In animal reproduction studies, administration of ribociclib to pregnant animals during organogenesis resulted in increased incidences of postimplantation loss and reduced fetal weights in rats and increased incidences of fetal abnormalities in rabbits at exposures 0.6 or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600 mg/day based on AUC *[see Data]*. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ribociclib up to 1000 mg/kg/day and 60 mg/kg/day, respectively, during the period of organogenesis.

In rats, 300 mg/kg/day resulted in reduced maternal body weight gain and reduced fetal weights accompanied by skeletal changes related to the lower fetal weights. There were no significant effects on embryo-fetal viability or fetal morphology at 50 or 300 mg/kg/day.

In rabbits at doses ≥ 30 mg/kg/day, there were adverse effects on embryo-fetal development including increased incidences of fetal abnormalities (malformations and external, visceral and skeletal variants) and fetal growth (lower fetal weights). These findings included reduced/small lung lobes, additional vessel on the descending aorta, additional vessel on the aortic arch, small eyes, diaphragmatic hernia, absent accessory lobe or (partly) fused lung lobes, reduced/small accessory lung lobe, extra/rudimentary 13^{th} ribs, misshapen hyoid bone, bent hyoid bone alae, and reduced number of phalanges in the pollex. There was no evidence of increased incidence of embryo-fetal mortality. There was no maternal toxicity observed at 30 mg/kg/day.

At 300 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal systemic exposures (AUC) were approximately 0.6 and 1.5 times, respectively, the exposure in patients at the highest recommended dose of 600 mg/day.

8.2 Lactation

Risk Summary

It is not known if ribociclib is present in human milk. There are no data on the effects of ribociclib on the breastfed infant or on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats. Because of the potential for serious adverse reactions in breastfed infants from KISQALI, advise lactating women not to breastfeed while taking KISQALI and for at least 3 weeks after the last dose.

Data

In lactating rats administered a single dose of 50 mg/kg, exposure to ribociclib was 3.56-fold higher in milk compared to maternal plasma.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal studies, KISQALI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Females of reproductive potential should have a pregnancy test prior to starting treatment with KISQALI.

Contraception

Females

Based on animal studies, KISQALI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with KISQALI and for at least 3 weeks after the last dose.

Infertility

Males

Based on animal studies, KISQALI may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1) in the full prescribing information]*.

8.4 Pediatric Use

The safety and efficacy of KISQALI in pediatric patients has not been established.

8.5 Geriatric Use

Of 334 patients who received KISQALI in Study 1, 150 patients (45%) were ≥65 years of age and 35 patients (11%) were ≥75 years of age. No overall differences in safety or effectiveness of KISQALI were observed between these patients and younger patients.

8.6 Hepatic Impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh A). A reduced starting dose of 400 mg is recommended in patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) *[see Dosage and Administration (2.2) in the full prescribing information]*. Based on a pharmacokinetic trial in patients with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib. The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (geometric mean ratio [GMR]: 1.50 for C_{max}; 1.32 for AUC_{inf}) and severe (GMR: 1.34 for C_{max}; 1.29 for AUC_{inf}) hepatic impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

10 OVERDOSAGE

There are no known cases of overdose with KISQALI. General symptomatic and supportive measures should be initiated in all cases of overdose where necessary.

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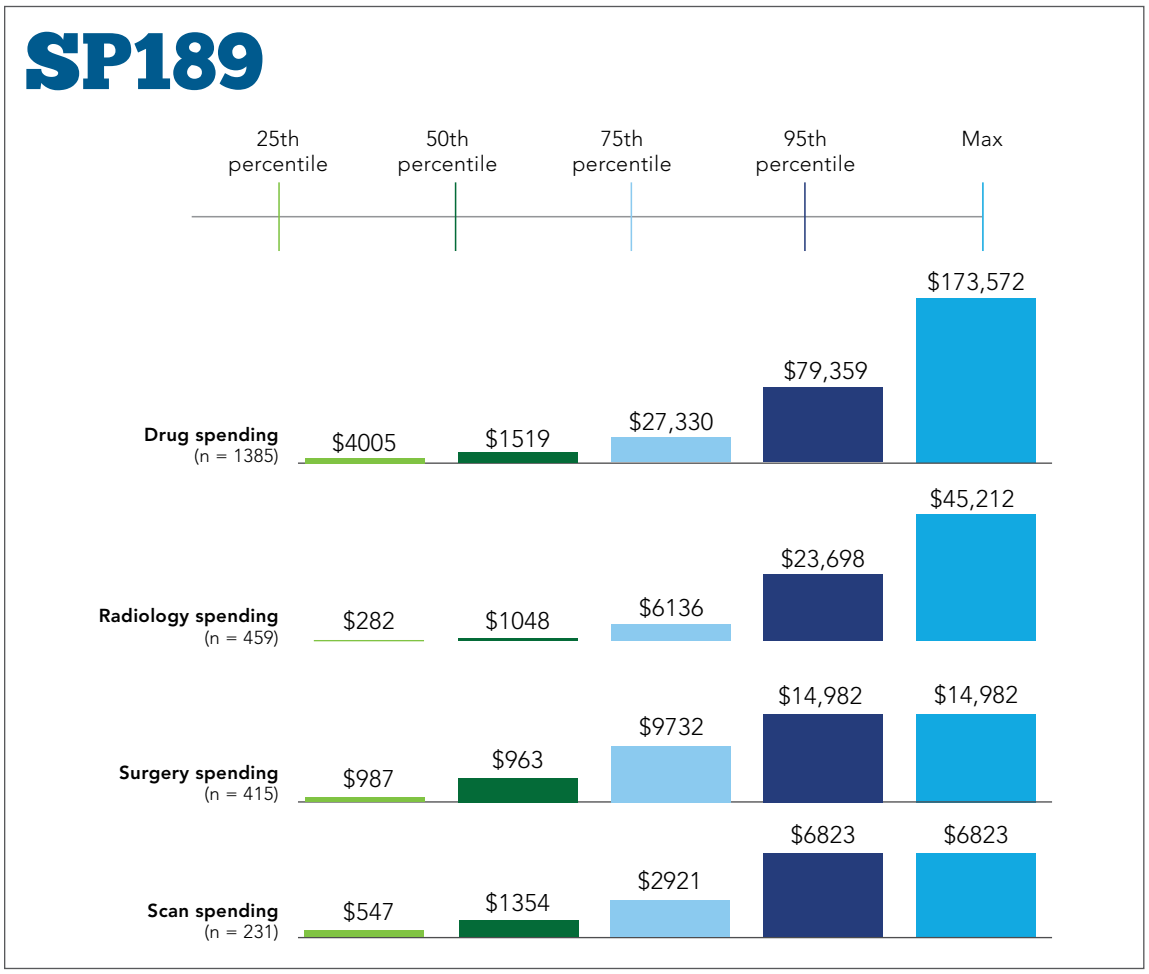

Source: Deloitte analysis of 2013-2014 Truven MarketScan commercial claims data for stage 1 breast cancer patients, episodes starting from first dose of chemotherapy plus 6 months.

FEATURES

INSIDE THE ISSUE

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FROM THE CHAIRMAN

Do We Have a Successful Reimbursement Model in Oncology?

MIKE HENNESSY, SR

ACROSS THE HEALTHCARE SPECTRUM, health plans—both federal and private—and physician organizations have been developing care delivery and payment models that comply with CMS' goals for value-based care. Within oncology, for example, multiple practices and 17 private payers are participating in the Oncology Care Model (OCM), an episode-based payment model for chemotherapy administration, developed by the Center for Medicare & Medicaid Innovation. OCM has incorporated a 2-part payment system that pays physicians a fixed monthly fee and a performance-based fee per episode of care.

However, because poorly designed alternative payment models (APMs) can shift the financial risk to physicians for things they cannot control, Harold D. Miller, head of the Center for Healthcare Quality and Payment Reform, believes that the priority should be to improve cancer care delivery. Suitable APMs can be designed to overcome current payment barriers and to enable oncology practices to deliver better care to patients and save money for payers in ways that are financially sustainable for the practices.

Anticipating the need for a payment model that compensates oncologists for providing oncology care in a high-quality, patient-centered fashion, the American Society of Clinical Oncology developed its *Patient-Centered Oncology Payment (PCOP)* model. In their article in this issue, oncologists who were actively involved in developing PCOP express hope that this new model will be accepted by CMS as an advanced APM and become available to medical oncologists as an alternative to the Merit-based Incentive Payment System program.

Pointing out deficits in Medicare's payment policies for hospital inpatient bone marrow transplants, Jeffrey W. Chell, MD, who heads the National Marrow Donor Program, explains that payment and access issues continue to cause anxiety for patients enrolled in Medicare who choose to undergo bone marrow transplant in an inpatient facility. While healthcare policies complement advances in medical technology, payment policies have been lagging. Chell strongly urges CMS to change its policies so Medicare beneficiaries do not face coverage hurdles related to the site where they choose to receive care.

Experts from the Deloitte Center for Health Solutions share the results of their interviews with individuals from health plans, providers, and clinical pathway developers that are participating, supporting, or evaluating oncology payment models. "Many stakeholders across the ecosystem are investing in new technologies, such as artificial intelligence and blockchain, to help illuminate which drugs work in specific patient populations and under what circumstances. Access to such information could guide the use of new drugs and treatments, improve health outcomes, and reduce spending," they write.

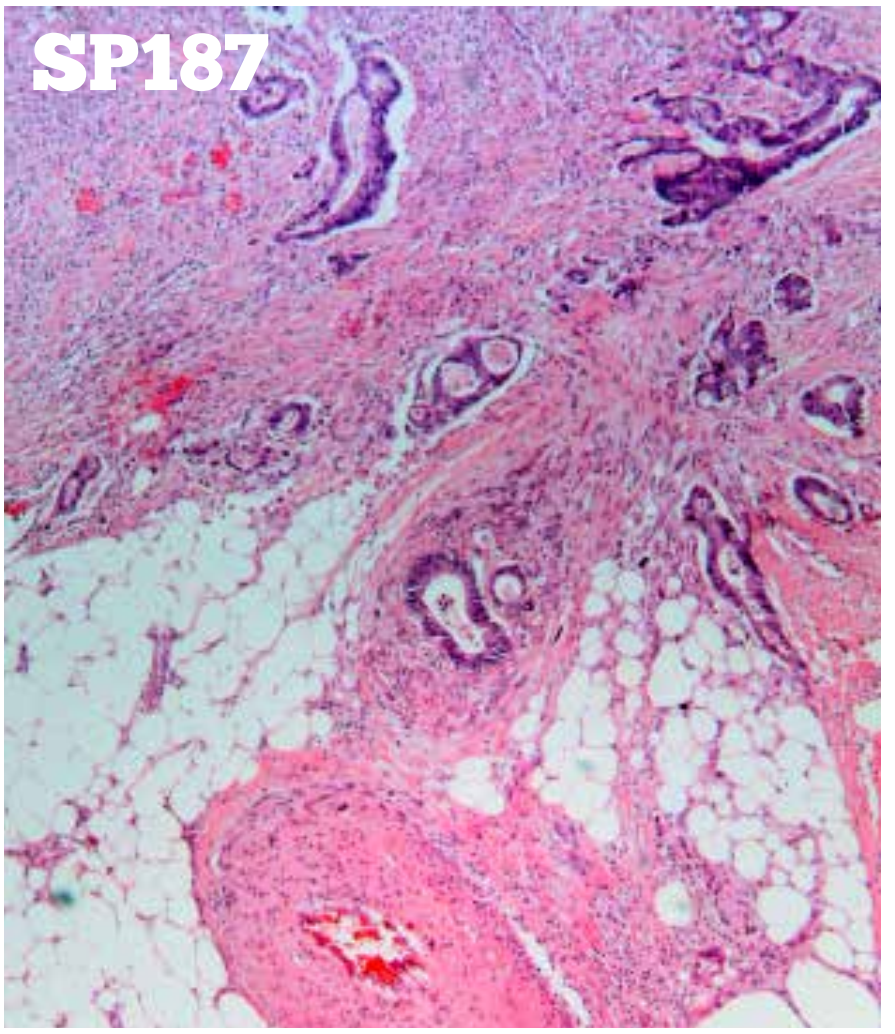
With changes in healthcare a new constant, we hope that our focus on payment models in this issue of *Evidence-Based Oncology*™, will prove beneficial to our readers. Thank you for your readership, and please visit www.ajmc.com for the latest updates in healthcare news and research. ◆

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

CONTENTS (CONTINUED)

APRIL 2017 VOLUME 23 ISSUE 5



TUMOR INVASION INTO VEIN IN A CASE OF COLORECTAL CANCER

FROM THE EDITOR IN CHIEF

Transparency and Collaboration Key to the Success of Value-Based Payment Models

Joseph Alvarnas, MD

JOSEPH ALVARNAS, MD

DESPITE ATTEMPTS BY GOVERNMENT, healthcare systems, and payers to rein in costs, healthcare expenditures in the United States continue to grow at a significant rate. In 2015, total US healthcare spending rose to $3.2 trillion, or a cost of nearly $10,000 per person.[1] Despite attempts, legislated through the Affordable Care Act, to reduce this growth, healthcare–related inflation actually increased from 4.6% in 2014 to 5.8% in 2015—a rate that is nearly 5-times that of inflation for the American economy overall.[2]

In addition to this increase in aggregate costs, pharmaceutical costs grew by 9% and out-of-pocket health-related spending rose by 2.6%.[1] This astronomical (and growing) level of spending, begs the question, "What kind of healthcare are we getting for over $3 billion?" Our inability to answer this question easily, consistently, and transparently across different healthcare systems and payer networks reflects how difficult it is to assess value in healthcare delivery.

Value has become a catchword in healthcare, and this has been true for a while already within the domain of cancer care, where the extraordinary complexity and intensity of effective care, coupled with the astronomical prices of new anticancer agents, have led many to question the economic sustainability of delivering effective and innovative care to this population of patients. Everyone, from payers to employers to professional societies (such as the American Society of Clinical Oncology)[3] and consortia of experts (such as the National Comprehensive Cancer Network),[4] has tried to tackle the protean tasks of describing and assessing value in cancer care. None of these major stakeholders has been particularly successful in developing a robust compelling system for assessing the value of care delivery for an individual patient or even for a diagnostically similar population of patients.

Although value is traditionally defined as cost/outcomes, it does a poor job of integrating clinical and diagnostic risks (including molecular, genomic, and proteomic data) into this value assessment. A further limitation is that the nebulous nature of cancer-related outcomes and the profound difficulty of capturing survival outcomes further undermine the degree to which value in cancer care can be reliably assessed. If overall value in healthcare is to be enhanced over time and costs controlled in a meaningful way that does not undermine the quality of cancer care for individual patients, there will need to be an unprecedented degree of transparency and collaboration among key stakeholders.

This issue of *Evidence-Based Oncology*™ attempts to describe how this can be accomplished through advances in data analytics, innovative payment models, addressing the rising costs of pharmaceuticals rationally, and ensuring that these efforts are supported through insightful public policy making. Sonal Shah, PharmD, and Greg Reh from Deloitte review value-based payment models from a multi-faceted stakeholder perspective. The team from Flatiron Health describes the importance of technology and data transparency in meeting the requirements of innovative payment models. Harold Miller discusses some of the alternative payment model opportunities for physicians that may allow for the development of more effective at-risk models for healthcare payment. S. Mantravadi, PhD, MS, MPH, from the University of West Florida, tries to place the rising cost of effective, new pharmaceutical agents in the context of improved patient outcomes.

Inasmuch as the task of describing value delivery in cancer care seems to grow in complexity the closer that we examine it, this is essential in order to both rationally control the growth of healthcare costs and ensure that we do not undermine the care of the patients whom we serve. We will continue to revisit this issue over time and invite you to be part of this ever-evolving conversation. ◆

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EDITORIAL MISSION

To present policy makers, payers, and providers with the clinical, pharmacoeconomic, and regulatory information they need to improve efficiency and outcomes in cancer care.

More patients, more complex therapies, more patient access barriers, more payer requirements—the demands on independent practices grow daily. Turning this chaos into order takes distribution services built around practice workflow and technologies that create more time with patients. It takes clinically integrated specialty pharmacy services that enhance patient care. The most effective specialty care takes the most efficient specialty practices. It takes AmerisourceBergen.

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How to Create Successful Alternative Payment Models in Oncology

Harold D. Miller

MILLER

Harold D. Miller is president and chief executive officer, Center for Healthcare Quality and Payment Reform.

The term "Alternative Payment Model" (APM) was added to the healthcare lexicon as a result of the passage of the Medicare Access and CHIP [Children's Health Insurance Program] Reauthorization Act (MACRA) in 2015.[1] Although MACRA is best known for repealing the Sustainable Growth Rate formula and creating the Merit-based Incentive Payment System (MIPS), Congress expressed a preference for APMs rather than MIPS by offering physicians a 5% bonus, higher annual updates, and exemption from MIPS if they participate at a minimum level in certain types of APMs.

What Is an APM?

MACRA defines an APM as "a model under section 1115A, the shared savings program under section 1899, a demonstration under section 1866C, or a demonstration required by Federal law." Section 1115A is the part of the Affordable Care Act (ACA) that created the Center for Medicare & Medicaid Innovation (CMMI).[2] It requires testing "payment and service delivery models…where… there is evidence that the model addresses a defined population for which there are deficits in care leading to poor clinical outcomes." The focus is to create models that are "expected to reduce program costs…while preserving or enhancing the quality of care received…" The law lists 24 models that CMMI is authorized to pursue, such as:

- "Establishing care coordination for chronically ill applicable individuals at high risk of hospitalization through a health information technology–enabled provider network that includes care coordinators, a chronic disease registry, and home telehealth technology," and
- "Aligning nationally recognized, evidence-based guidelines of cancer care with payment incentives…in the areas of treatment planning and follow-up care planning for… individuals…with cancer." [2]

Terms such as "bundle," "episode," "global payment," and "shared savings" do not appear anywhere in Section 1115A. It allows any payment model that will "improve the quality of care without increasing spending," "reduce spending …without reducing the quality of care," or "improve the quality of care and reduce spending."

Section 1899, which authorized the Medicare Shared Savings Program, states that its purpose is to create a program that "promotes accountability for a patient population and coordinates items and services under parts A and B, and encourages investment in infrastructure and redesigned care processes for high quality and efficient service delivery."[3] Most people are not aware that this section authorizes use of partial capitation and "other payment models" as well as shared savings, because CMS has not implemented these other approaches.

The law clearly indicates that the core element of a "model" is a method of improving *care delivery*, not simply a different method of *payment*.[2] It's called an "alternative" payment model because a) it must demonstrate it will not increase Medicare spending, and b) savings in Medicare Parts A or D can be counted, not just savings in Medicare Part B or physician fee-schedule services. The current requirement that new physician service payments must be accompanied by reduced payments for other physician services does not apply to APMs.

Why Would Physicians Want to Be Part of an APM?

Two important misperceptions about APMs are: 1) they are needed so physicians will have "incentives" to deliver care differently and 2) the only reason physicians would want to be in an APM is to be exempt from MIPS or to receive the bonuses Congress authorized. The reality is that many physicians want to deliver care in different and better ways, but cannot do so due to barriers in the current payment system. Two major barriers[4] are:

Lack of payment or inadequate payment for high-value services. Medicare and most health plans do not pay physicians for many services that would benefit patients and reduce spending, such as responding to patient phone calls or using nurses to help patients manage their health problems.

Financial penalties for delivering a lower-cost mix of services. Under fee-for-service (FFS) payment, physician practices that perform fewer or lower-cost procedures may no longer receive enough revenue to cover their practice costs. Today, physician practices are paid less when they help patients stay healthy enough to require fewer services.

A well-designed APM can overcome these barriers by paying adequately for high-value services and basing payment on the conditions or symptoms being managed and the outcomes achieved, rather than on the specific treatments used.

Another misperception is that physicians and other providers must accept significant financial risk for Medicare spending as part of an APM. Many physicians have been unable or unwilling to participate in existing APMs because of the high level of financial risk involved. However, sections 1115A and 1899 do not require that APMs impose financial risk on physicians. One of the only 2 models developed under Section 1115A that has been certified by the CMS Actuary for national expansion is the Diabetes Prevention Program, and there is no financial risk for providers in that model.[5]

What MACRA requires is that some entity accept "more than nominal financial risk" under an APM in order for a physician to receive a 5% bonus, higher annual update, and MIPS exemption. CMS was widely criticized for setting the "more than nominal" standard too high in its proposed regulations, and a more reasonable standard was included in the final rule. This will make it easier for physicians to participate in APMs that qualify for bonuses and the MIPS exemption. However, there can still be significant advantages to APMs that do not meet the risk requirements.

How APMs Could Help Improve Cancer Care

Rather than choosing payment models and forcing physicians to deliver care that fits the payments, MACRA and the ACA clearly wanted the process to start with changes in care delivery and have payment models designed to support those changes. There are many opportunities to improve cancer care that are not being addressed due to barriers in FFS payment, and well-designed APMs could help change this. Three such opportunities are:

1. Reducing hospital visits due to complications of chemotherapy. The benefits of chemotherapy are often accompanied by side effects, such as nausea, diarrhea, and neutropenia, that can lead to serious complications, such as, dehydration and infection. Many patients receiving chemotherapy go to emergency departments (EDs) for treatment of these complications, and they are often admitted to the hospital because of the severity of the complications.

Chemotherapy-related ED visits and hospitalizations represent a significant portion of overall spending on cancer care. A 2010 study estimated that commercial insurance plans spent more than $9000 per patient on chemotherapy-related ED visits and hospital admissions,[6] and a 2012 study of Medicare beneficiaries receiving cancer treatment found that risk-adjusted per-patient spending on hospitalizations varied by more than $3000 across the country.[7]

Two projects supported by CMMI grant funding have shown that significant reductions in ED visits and admissions can be achieved by redesigning the way care is delivered to patients receiving chemotherapy:

- The Patient Care Connect Program at the University of Alabama at Birmingham (UAB) Health System Cancer Community Network employed nonclinical patient navigators to screen for distress and encourage patients to seek early help from the oncology practice, rather than delay care or use the ED for non–life-threatening conditions.[8] The project significantly reduced ED visits and hospitalizations and achieved savings 10 times as great as the cost of the navigators.[9]
- In the Community Oncology Medical Home (COME HOME) project, an improved triage system and enhanced access to outpatient treatment enabled early, rapid, low-cost interventions, such as intravenous hydration when patients experienced chemotherapy-related complications. An independent evaluation showed significant reductions in ED visits, hospitalizations, and total cost of care for the patients.[10]

Most oncology practices can't implement these successful approaches for a simple reason: they can't afford to. Federal grants were needed to enable the UAB and COME HOME practices to implement these initiatives.

How could an APM enable these programs to continue after the grants end and allow other practices to replicate them? The simplest approach would be to make additional payments to cover the costs of the currently unbillable services in return for accountability by the oncology practice to achieve low rates of ED visits and hospitalizations for its patients. The 2 components of the APM would be:

- ***Flexible monthly payments to support enhanced services.*** A flexible payment could be used to employ patient navigators or triage nurses or to cover financial losses from keeping treatment slots open on the practice schedule. Since the payments are intended to avoid complications as well as to enable early treatment when complications arise, it is more appropriate to base the payment on the *patient*, rather than base the payment on the delivery of a specific *service* to that patient. A growing number of APMs make "per member per month" payments to physician practices so revenues aren't driven by the volume of services delivered.

- ***Adjustments to the payments based on performance in achieving outcomes.*** Since the purpose of the additional payments is to help avoid ED visits and hospital admissions, the risk-adjusted rate of visits and admissions for a practice would be measured, and if those rate(s) are higher than rates other practices had achieved with similar resources, the amount of the per-patient payment would be reduced.

This 2-part structure is different and better than most "value-based payment" models being used today:

- In MIPS and other pay-for-performance systems, the oncology practice receives no additional resources to deliver additional and better services, merely a small change in current FFS payments as an "incentive" to do something they can't afford.
- In shared savings models, the practice receives no up front resources to support different services. If it is already successful in controlling ED use, it won't qualify for the shared savings payments it may need to sustain the services that achieve that result.

MEDICARE SPENT MORE THAN $1.2 BILLION ON PEGFILGRASTIM INJECTIONS IN 2015, THE THIRD HIGHEST AMOUNT OF SPENDING ON ANY PART B MEDICATION.

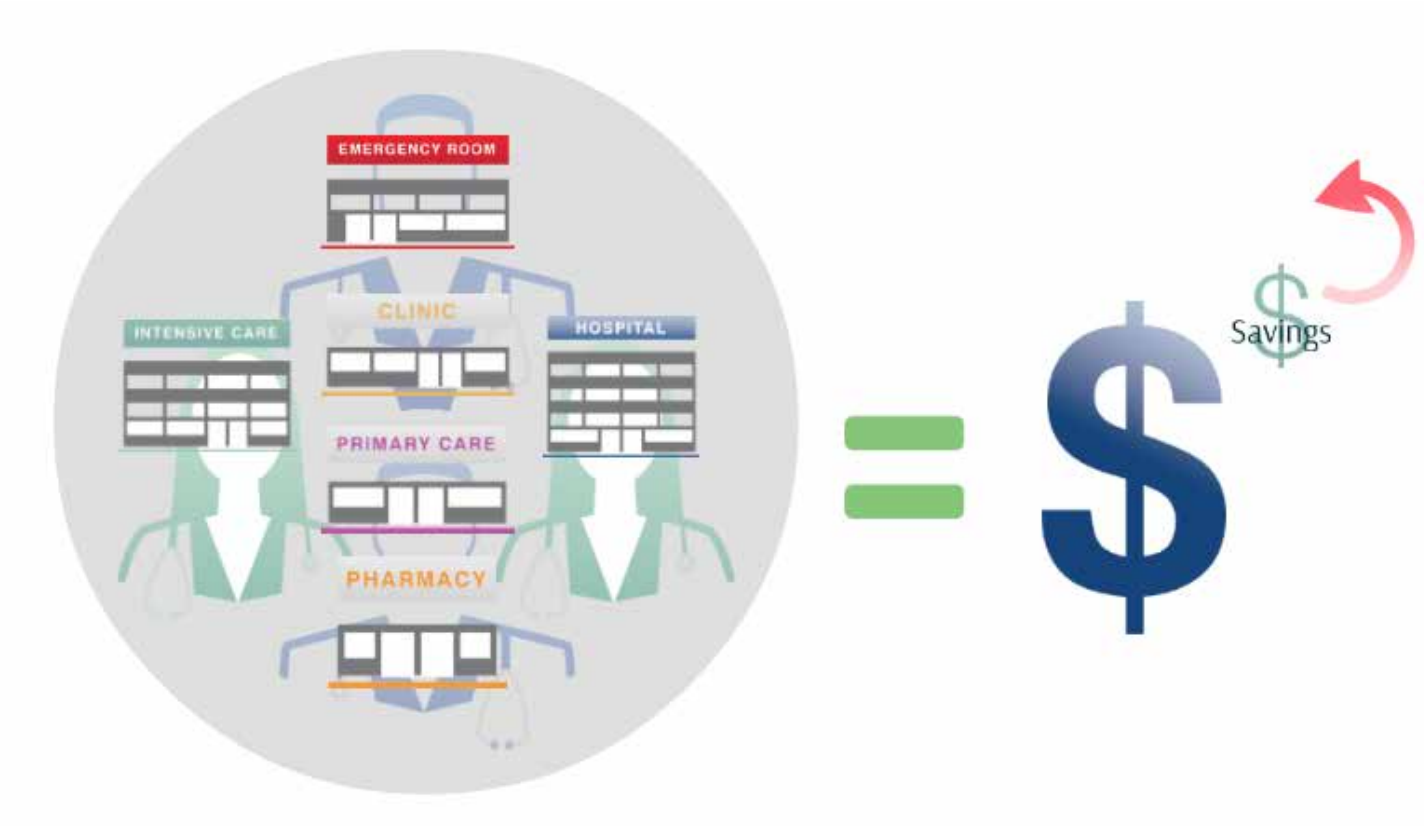
2. Improving end-of-life care. There is widespread concern about the number of cancer patients who receive treatments that will neither cure their disease nor prolong their lives, but will significantly diminish quality of life during their final months. These prolonged treatments can lead to poor end-of-life experiences for patients and families alike, as well as to very high expenses for payers.

Multiple studies have shown that palliative care services can significantly reduce ED visits, hospitalizations, and other avoidable services and the savings can more than offset the cost of the services.[11] However, once again, oncology practices don't offer palliative care services because they can't afford to. Medicare and most health plans will only pay for multidisciplinary in-home palliative care under a hospice benefit, and many patients and physicians aren't willing to completely terminate treatment and declare that the patient has only 6 months to live in order to qualify.

An APM could fill this gap. Once again, 1) a monthly payment could provide the resources an oncology practice or palliative care team need to provide good care and 2) a performance-based adjustment, based on rates of avoidable ED visits, hospitalizations, and procedures, would provide the accountability payers need to assure that overall spending will not increase. Instead of arbitrary eligibility criteria to limit spending, the monthly payment could be stratified based on patient needs, so the resources the oncology practice (or its palliative care team partner) receive are matched to the opportunities to improve care.

Most of the "episode" payment models being used today are triggered by delivery of a particular procedure, and they financially penalize a physician for not delivering that procedure when it is not needed. A better approach is a "condition-based payment" that bases payment on the patient's needs, not on how many or what types of services were delivered.[12]

3. Controlling drug spending. For most types of cancer, pharmaceuticals are a major component of overall spending on cancer treatment. Although high prices are a major reason for high drug »



THE FEE-FOR-SERVICE SYSTEM IS DRAINING THE HEALTHCARE SYSTEM, BECAUSE IT PAYS FOR VOLUME RATHER THAN VALUE OF CARE. WHAT WE ARE LEFT WITH IS UNCOORDINATED CARE, DUPLICATION OF SERVICES, AND FRAGMENTATION.

spending, there are opportunities beyond price reductions to reduce drug spending.

For example, one of the biggest sources of Medicare drug spending in cancer care in recent years wasn't a chemotherapy drug, it was pegfilgrastim, which is used to stimulate production of white blood cells to reduce the chance of infection resulting from chemotherapy. Medicare spent more than $1.2 billion on pegfilgrastim injections in 2015, the third highest amount of spending on any Part B medication.[13] The drug is very expensive, averaging more than $13,000 per patient in 2015.

Although white-cell stimulating factors (CSFs) such as pegfilgrastim can help prevent serious infections when patients receive highly toxic chemotherapy, the drugs can also produce severe bone pain and other side effects. The American Society of Clinical Oncology issued a Choosing Wisely guideline recommending use of CSFs for primary prevention of febrile neutropenia only for chemotherapy regimens with a 20% or higher risk of the complication.[14]

POORLY DESIGNED APMS THAT SHIFT FINANCIAL RISK TO ONCOLOGISTS FOR EVENTS THEY CANNOT CONTROL COULD CAUSE SERIOUS HARM TO PATIENTS.

Two recent studies, in different parts of the country and for Medicare and commercially insured patients, found only 70% adherence to the Choosing Wisely guideline.[15,16] If 30% of the patients getting the drug don't really need it, that could represent $400 million in savings for the Medicare program—the same amount that would be saved if the price of every Part B drug was 2% lower.

An APM could help achieve these savings while protecting patients. The Choosing Wisely recommendation is a guideline, not an absolute rule. Flexibility is needed to address individual patient needs, and if a patient doesn't receive a CSF, the oncology practice needs effective systems to monitor the patient and respond to problems quickly—the kinds of services described earlier that are not compensated under current FFS payments. Moreover, maintaining the guideline over time requires tracking 1) use of the CSF, 2) complication rates associated with new chemotherapy regimens, and 3) the effectiveness of new CSFs that enter the market. Since these are all costs that are not paid for today, the APM could 1) pay a per-patient amount that the practice could use to cover these costs in return for 2) the practice documenting adherence to the guideline and the reasons for deviations.[17]

What About the Oncology Care Model?

In 2016, CMMI contracted with 190 oncology practices to implement an APM called the Oncology Care Model (OCM). OCM has a 2-part payment structure similar to what is described above: a monthly payment for each patient receiving chemotherapy and a performance-based payment.[18] However, the details of the design create concerns for both oncology practices and patients:

- The performance-based payment is based on whether *total* spending on the patient is higher or lower than a CMS-defined target. This places the practice at risk not just for ED visits and hospitalizations, but also for things beyond its control, such as treatments for health problems other than cancer, increases in drug prices, etc.[19]
- The target spending level is not adjusted based on how many patients are receiving highly toxic regimens, nor are there quality measures to ensure that patients receive CSFs when appropriate. This means that practices could receive financial rewards for failing to administer expensive drugs, such as pegfilgrastim, to patients who need them.
- Monthly payments are only for patients receiving chemotherapy, making it impossible to pay for palliative care after treatment ends. Moreover, the higher payment creates a perverse incentive to continue using chemotherapy.

In contrast, the CMMI Comprehensive Primary Care Plus (CPC+) payment model has flexible monthly payments and

adjustments based on performance without creating similar problems.[20] Primary care practices receive per-beneficiary-per-month and performance-based payments, but the practice receives the performance-based payment in advance. Payments are reduced only if the rates of ED visits or hospitalizations are high; reductions are not based on total spending. CMS has certified that the CPC+ APM would meet the "more than nominal financial risk" standards under MACRA, so primary care physicians in that model would qualify for the 5% bonus, higher updates, and exemption from MIPS.

Creating Physician-Focused APMs

Clearly, well-designed APMs can help oncology practices deliver better care to patients and save money for payers in a way that is financially sustainable for the practices. In contrast, poorly designed APMs that simply shift financial risk to oncologists for events they cannot control, or that fail to provide the resources needed to deliver better care, could cause serious harm for patients.

There is no ideal APM design. Some practices, particularly small ones, may only be able to tackle 1 change at a time, and more narrowly focused APMs will work better for them. Other practices may prefer broader condition-based APMs in order to make more improvements simultaneously.

Congress indicated it wants physicians, not payers, to take the lead in designing APMs by creating a special process for encouraging the development and implementation of "physician-focused payment models."[21] Now, cancer care providers who develop better ways of delivering care can also design solutions to the payment barriers that prevent implementation of those changes and submit their proposals to the Physician-Focused Payment Model Technical Advisory Committee for consideration.[22] This creates a much-needed opportunity to accelerate the development and implementation of value-based payment systems that will benefit patients, payers, and providers. ◆

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#1 PRESCRIBED ORAL CLL THERAPY.*
MORE THAN 20,000 PATIENTS TREATED SINCE APPROVAL[1†]

MAKE IMBRUVICA® YOUR FIRST STEP

Approved in frontline CLL with or without 17p deletion[2]

CLL
SLL

IMBRUVICA® is a once-daily oral therapy indicated for:

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in 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 therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this

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 02/17 PRC-02652

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)

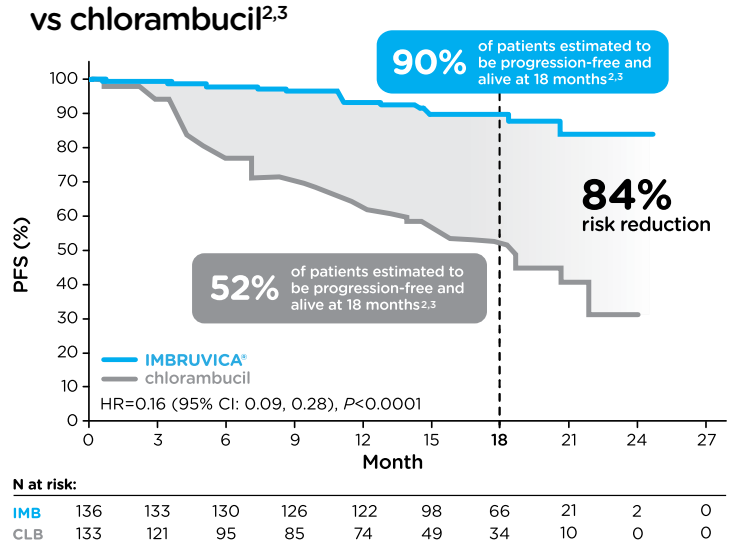
84% chlorambucil
(95% CI: 77, 90)

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

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.

*Based on market share 2016 July YTD data from IMS.
†Based on IMS data February 2014 to date.

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 leukemia.

References: 1. Data on file. Pharmacyclics LLC. **2.** IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC 2017. **3.** Burger JA, Tedeschi A, Barr PM, et al; for the RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.

To learn more, visit
IMBRUVICAHCP.com

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

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1 (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies*	12*	0
Vascular disorders	Hypertension	16	8

* One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL/SLL (N=51) in Study 1

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

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

Study 2: Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in Study 2 in patients with previously treated CLL/SLL.

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

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

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

Table 6: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL/SLL in Study 2

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

* Based on laboratory measurements per IWCLL criteria.

Study 3: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in Study 3.

IMBRUVICA® (ibrutinib) capsules

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in Study 3

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
Eye Disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular Disorders				
Hypertension*	14	4	1	0
Nervous System Disorders				
Headache	12	1	10	2

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

Study 4: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in Study 4 in patients with previously treated CLL/SLL.

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in Study 4

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

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

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

Waldenström's Macroglobulinemia and Marginal Zone Lymphoma: The data described below reflect exposure to IMBRUVICA in open-label clinical trials that included 63 patients with previously treated WM (Study 5) and 63 patients with previously treated MZL (Study 6).

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.

IMBRUVICA® (ibrutinib) capsules

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.

POLICY

An Oncologist's Perspective: Preparation for New Payment Models in Cancer Care

Sachin M. Apte, MD, MS, MBA

Introduction

In 2013, the Institute of Medicine (IOM; now called The National Academy of Medicine) described a cancer care delivery system in crisis.[1] The stress on our healthcare system is amplified by an aging population, healthcare workforce shortage, and rising costs. By 2020, the cost of cancer care is estimated to be $173 billion, a staggering 39% increase over 2010 levels. In a 2001 report, Crossing the Quality Chasm, the IOM described 6 aims for healthcare: safe, effective, patient-centered, timely, efficient, and equitable.[2] Components of the 13 IOM recommendations directly address issues such as providing high-quality, evidence-based care; sharing health information; improving processes of care; using resources efficiently; coordinating care; and redesigning payment methods to incentivize quality enhancement and remove barriers that impede quality improvement.[2] In the 16 years since the publication of Crossing the Quality Chasm, several key issues have remained unresolved and barriers to improving quality and value in oncology have persisted. The Quality Payment Program (QPP) by CMS aims to drive further transformation forward in oncology.

The care for a patient afflicted with cancer is complex, resource-intense, and constantly evolving. These challenges are compounded by the changes underway in physician payment reform. It is critical that oncologists and leaders of hospitals and healthcare systems comprehend these changes to successfully adapt and remain agile while providing high-quality, compassionate, and timely care to patients with cancer. In parallel with the QPP, cancer care providers need to develop comprehensive, individualized, and forward-thinking strategies to successfully adapt to new payment models in oncology. Such strategies may necessitate workflow changes that must be tracked.

Quality Payment Program

Strong bipartisan support for the Medicare Access and CHIP [Children's Health Insurance Program] Reauthorization Act (MACRA) in 2015 led to the final rule being published in October 2016. MACRA, rebranded as QPP, includes 2 tracks:

- The Merit-based Incentive Payment System (MIPS)
- Advanced alternative payment models (APMs)
- MIPS, which includes Medicare Part B payments and excludes Part A (hospital payment), combines portions of existing programs into a single composite score. The legacy programs include the Physician Quality Reporting System, "Meaningful Use," and the Value-based Payment Modifier. For 2017, the score for the 4 MIPS categories will be weighted as follows:
- Improvement activities (IAs), 15%
- Advancing care information (ACI), 25%
- Quality, 60%
- Cost, 0%

It is important to note that the weighting will change over time: by 2019, both quality and cost will be weighted at 30%. CMS' QPP interactive website contains tools and information for providers and hospitals.[3] For 2017, providers may choose not to participate, but will receive a 4% »

APTE

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payment reduction. Submission of at least 1 quality or IA metric, or the required ACI metrics, will avoid any penalties. The provider may choose to submit data for 90 consecutive days or an entire year. Submitting all MIPS data for at least 90 days may result in up to a 4% increase plus a performance bonus. For the first MIPS payment year in 2019 (performance year 2017), payment adjustments will be at ±4% based on the MIPS composite score, and by 2022, the adjustment will be at ±9%.

Advanced APMs provide incentives to promote high-quality and cost-efficient care for a specific condition, defined episode, or a population. Advanced APMs require use of certified electronic health record (EHR) technology; they tie payment to quality and entail downside financial risk. A subset of advanced APM participants, defined as Qualifying Professionals (QPs), will see a 5% increase in Part B payments from 2019 to 2024, be exempt from MIPS, and will have higher base rates beginning in 2026. In 2019, QPs must meet minimum requirements of defined percentages of Medicare payments and patients (25% and 20%, respectively) coming through the advanced APM. For 2023 and beyond, the payment and patient thresholds increase to 75% and 50%, respectively. Advanced APM participants who do not satisfy the QP requirements may still receive favorable MIPS scores.

Physician-Focused Payment Model Technical Advisory Committee

MACRA incentivizes physicians to participate in APMs, including the development of physician-focused payment models (PFPMs). The Physician-Focused Payment Model Technical Advisory Committee (PTAC), created by MACRA, provides recommendations to the HHS secretary on proposals for PFPMs. Ten criteria are used to assess a proposed PFPM, including an emphasis of value over volume, care coordination, defined quality and cost components, and whether the PFPM will expand the existing scope for APMs. The PTAC mechanism may be an opportunity for advanced APM development for subspecialty societies, large community-based multi-specialty groups, and tertiary cancer centers.

THE CARE FOR A PATIENT AFFLICTED WITH CANCER IS COMPLEX, RESOURCE-INTENSE, AND CONSTANTLY EVOLVING.

Strategic Considerations for QPP Implementation

Although MIPS may appear to represent a rebundling of existing programs, the mounting financial penalties for sub-optimal MIPS composite scores may push providers into an APM over the next several years. The assumption of risk could usher in dramatic changes as providers assess the scale of their operations and place a premium on care coordination and resource management. These changes will force oncologists to develop or acquire the necessary subject matter expertise. At Moffitt Cancer Center in Tampa, Florida, a multi-disciplinary team meets regularly to share information and begin building institutional knowledge, with outside consultation obtained in a targeted manner. This knowledge must be disseminated throughout the practice or organization to facilitate the change management required for QPP implementation. Successful adaption to new payment models will rely heavily on strategy, and subsequent workflow changes can then be designed to deploy strategy. The 6 issues listed below can help inform the organization's multi-disciplinary team as it starts designing a strategy.

1. Determine if a cancer care provider qualifies. A provider is part of the QPP if it participates in an advanced APM or bills Medicare Part B more than $30,000 a year and provides care for more than 100 unique Medicare Part B patients a year.[3] MIPS-eligible providers include:

- Physicians
- Physician assistants
- Nurse practitioners
- Clinical nurse specialists
- Certified registered nurse anesthetists.

At Moffitt, these nonphysician mid-level providers are an integral and large part of our care team. Their impact must be accounted for, a difference from prior physician-focused federal programs, such as Meaningful Use.

2. Determine a 2017 reporting period. Providers have an option to choose their pace for 2017. While reporting began on January 1, 2017, a provider who wants to participate in a limited fashion can begin reporting by October 2, 2017. Providers may opt not to report, submit a minimum amount of data (ie, 1 quality measure), report on 90 days of data, or submit data for an entire year. Data submission is due by March 31, 2018. Although the reporting year is 2017, the payment adjustment is made on January 1, 2019.

3. Determine if the provider should participate as an individual (National Provider Identifier) or report as a group practice under a single Tax Identification Number. There are pros and cons to individual versus group reporting. Individual reporting allows oncologists to choose the most relevant and meaningful quality metrics so that they can have an impact on the quality component of the MIPS score, in addition to having the potential for greater cost control. Group reporting, on the other hand, lets providers distribute the administrative burden associated with QPP participation. A bigger practice, for instance, may be better positioned to absorb financial penalties resulting from a poor performance.

4. Decide on MIPS versus advanced APM participation. CMS expects a majority of eligible clinicians to initially enroll in MIPS. Currently, the only oncology-specific advanced APM is the Oncology Care Model (OCM), which focuses on chemotherapy administration. Stakeholders who want to be considered for an advanced APM also have the option to submit an application to PTAC.[4]

5. Evaluation of reporting mechanisms. CMS requires that data be submitted using an approved method, depending on the metric. The Quality, ACI, and IA metrics can be reported via a Qualified Clinical Data Registry (QCDR), Qualified Registry, EHR, or Web interface with CMS (for groups of 25 or more). Attestation can be used for ACI and IA.[5]

For bigger groups, Quality can be reported via Consumer Assessment of Healthcare Providers and Systems. Potential costs associated with the chosen reporting mechanisms will need to be accounted for. In addition to data submission, some QCDRs may be able to provide modeling to optimize selection of metrics based on historic performance.

6. Provider employment model. The provider's model of employment may weigh heavily on the approach to QPP implementation. A self-employed provider or independent single-specialty practice will have inherently different considerations than a hospital-employed provider in a large multispecialty group practice. For example, a smaller-scale practice will have more autonomy in selecting quality metrics and improvement activities that are

aligned with the practice. Alternatively, a large-scale practice may incur an administrative burden that is less significant per provider and it will have more ability to accept and absorb downside risk. A large practice may also have greater access to sophisticated analytics and more data to better inform decisions. Regardless of the employment situation for an oncology provider, it is important that the providers communicate effectively with the affiliated hospital, such that efforts are aligned and coordinated. At Moffitt, early efforts are focused on integration of strategy across the enterprise to account for downstream impacts of actions on both the medical group and hospital operations.

Workflow Considerations for MIPS Implementation

Oncology providers will need to select metrics to report on 3 categories. The fourth category, cost, is claims-based. Below are the 4 categories that now constitute the MIPS composite score. The CMS QPP website displays this information, with filters, to aid providers.

1. ***Quality.*** Determine which 6 quality metrics will be most appropriate for your oncology practice (5 process and 1 outcome). Ensure that the reporting mechanism is validated, such as via an approved third-party vendor. Consider adding back-up metrics in case there are obstacles to reporting and to optimize overall performance. Close communication between the informatics and clinical care teams may help align efforts and confirm that there is a mechanism to capture data in a discrete and automated fashion to facilitate reporting metrics in a compliant manner.
2. ***ACI.*** The ACI metric includes 3 subsections. Choose to submit up to 9 measures: protecting health information, e-prescribing, health information exchange (HIE), providing patient access, patient education, view/download/transmit, secure messaging, medication reconciliation, and an immunization registry. In order to optimize performance, certain metrics may require changes in workflow. For example, for HIE, workflow changes may need to be made to establish secure connections with outside entities.
3. ***IA.*** Select 4 IAs for your individual or group practice (2 medium and 2 high) that have strategic importance to your organization. These IAs are attestations. Several of the CMS IA choices align with planned improvement efforts at Moffitt.
4. ***Cost.*** Although cost will not be a component of MIPS in 2017, oncologists can work with their financial analytics team to better understand the baseline information of the practice so it will be better prepared for 2018 and beyond. The Quality and Resource Use Reports can provide benchmarked data with respect to quality and cost, based on prior selection of quality metrics.[6] Other initial strategies can focus on developing an understanding of unnecessary care variation. Working off common care pathways may help dampen unnecessary variation when possible. Due to the heterogeneity inherent in complex cancer patients, pathway adherence can be challenging.

Workflow Considerations for Advanced APM Implementation

The first step is to determine if the practice is eligible for an advanced APM and satisfies necessary criteria. The OCM is the only advanced APM offered by CMS for cancer care; it has a focus on chemotherapy. OCM participation requires providers to first meet the standard advanced APM requirements, such as 24/7 access to a qualified provider and medical records, monitoring of data to improve quality, and use of EHRs. In addition, OCM participants must provide patient navigation, document a 13-point care plan using the IOM recommendations, and provide care consistent with recognized guidelines.[7] Payment is based on quality measures similar to those of MIPS.

An advanced APM requires assumption of a more-than-nominal financial risk. When implementing a bundled payment arrangement, there are 3 major categories to consider: degree of physician alignment, operational preparedness and maturity, and engagement of a payer partner.[8] For the purposes of this discussion, the payer is the federal government: arrangements with a commercial payer may have more flexibility.

1. Physician alignment. Alignment and engagement within the relevant group of oncology providers and between providers and their affiliated hospital is paramount. The decision to participate in an established advanced APM, or to develop one through the PTAC mechanism, depends on the active and willing participation of affected physicians. Advanced APMs may include payments that span the services of multiple providers and ancillary services, and there may be downstream impacts for the hospital. Physicians, in conjunction with the hospital, will need to develop the scope of services for the APM and agree on protocols. Hospitals will require resources and expertise to perform complex clinical and financial analytics to understand the major factors and variables impacting the total cost of care. Oncologists will need to commit to dampen unnecessary variation in a multitude of evaluation and management decisions. While oncologists need to put the patient first and provide high-quality, evidence-based care, minimizing unwarranted testing and treatment should be emphasized and there should be provision for some degree of predictability.

The concept of taking on financial risk in medicine is particularly challenging for oncologists who understand the tremendous heterogeneity in cancer care and the potential for catastrophic clinical and financial impacts. Even in a well-defined population of patients with cancer with a narrow scope of services, outliers exist at a greater frequency and magnitude compared with more common conditions in population management. The relationship between the oncologist and hospital will also vary based upon local factors, past experiences, a model for employment and incentive compensation, and the quality of the leadership from both the physicians and hospital.

2. Operational preparedness. *Financial risk analysis and management.* An important step is to perform modeling and sensitivity analyses to develop a clear picture of financial risk. Define, for example, the most significant and modifiable sources of risk and the potential frequency and magnitude of risk (eg, readmissions, pharmacy, length of stay, etc). Once a provider, group, or healthcare system enters into a risk-based arrangement, the provider must actively manage risk or else face an increased probability of either poor quality or inefficient resource utilization. This will likely require robust concurrent utilization review and a fully actualized and optimized case management program. Such strategies need to address »

AT MOFFITT, EARLY EFFORTS ARE FOCUSED ON INTEGRATION OF STRATEGY ACROSS THE ENTERPRISE TO ACCOUNT FOR DOWNSTREAM IMPACTS OF ACTIONS ON BOTH THE MEDICAL GROUP AND HOSPITAL OPERATIONS.

issues such as unnecessary or inefficient testing, post acute care partnerships, palliative care services, and the capability and capacity to manage emergency care to minimize treatment with providers outside the APM.

Management of catastrophic outcomes or incorporating new resource-intense therapies requires consideration of stop-loss provisions or carve-outs. Risk tolerance should be defined and will vary based on the scale of enterprise, overall financial health, and APM scope. Implementation of an advanced APM will also incur a large administrative task of tracking patients, which will require constant diligence to assure efficient resource use and preventing unwarranted variation. Consistent and transparent provider feedback may enable successful implementation of the APM and improved cancer care management.

3. Flow of funds. For an advanced APM spanning multiple providers and their hospitals, all parties must agree upon and understand the flow of funds, which should be distributed equitably—not just between hospital and oncology care provider, but among all the specialties and ancillaries involved. The following questions need up front clarification:

- Will there be a shared savings component? How will it be disbursed?
- What will be the attribution methodology for poor performance (either quality or cost) with downside risk? What are the financial repercussions for each party involved?
- Will payment be prospective or retrospective, especially for future APM arrangements via PTAC?

THE ASSUMPTION OF RISK COULD USHER IN DRAMATIC CHANGES AS PROVIDERS ASSESS THE SCALE OF THEIR OPERATIONS AND PLACE A PREMIUM ON CARE COORDINATION AND RESOURCE MANAGEMENT.

Research and Education: Mission Critical

Research and education are more important than ever in oncology. The pace of change in the understanding of the mechanisms of cancer continues to accelerate. For example, recent advances in immunotherapy and targeted therapies will benefit an increasing number of patients. Such advances are enabled by partnerships that include the pharmaceutical industry, academic medical centers, and community providers. Innovative research, however, comes at a cost, and cutting-edge treatment is often more expensive than standard-of-care treatment. New payment reforms must allow oncologists and scientists to innovate and improve outcomes without risking insolvency and irrelevance. The complexity of modern treatments demands years of rigorous training, and funding educational missions is critical to the development of a capable future workforce with sufficient capacity to meet the growing need.

An Uncertain Road Ahead

The QPP is designed to accelerate the transition from volume- to value-based payments, with a focus on quality outcomes, efficient resource utilization, and, ultimately, the assumption of risk. Stakeholders have significant concerns, including that the QPP is burdensome and complex, MIPS measures are not applicable or meaningful, and advanced APM options are limited. Other concerns relate to attribution, particularly with the quality and cost components of these payment models.

Cancer patients frequently receive care across different providers or health systems. Additionally, the duration of time between diagnosis, treatment, and outcome is often quite long. Therefore, attribution requires thoughtful and careful consideration. In late 2016, the Office of the Inspector General performed an early implementation review of the QPP and cited 2 vulnerabilities: providing sufficient guidance and technical assistance to eligible clinicians; and developing adequate information technology systems for reporting, scoring, and making adjustments. With leadership changes at HHS and CMS, changes to the QPP are possible. Nonetheless, the basic tenets of payment reform are likely common to any healthcare leadership.

Regardless of the uncertainty ahead, there is value in understanding and implementing the QPP, as the experience gained will be applicable to any future payment system aimed at pursuing value-driven care in oncology. Federal regulations will change and providers will need to pivot, but the needs of patients diagnosed with cancer will not stop. Despite the challenges posed by a dynamic cancer care landscape, the duties of an oncologist will remain to treat, cure, and comfort patients afflicted with an often relentless disease that is not beholden to any legislation. ◆

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CMS Needs to Address Medicare Underfunding in 2017 Hospital Inpatient Rule for Bone Marrow Transplantation

Jeffrey W. Chell, MD

Blood Cancers and the Evolution of Hematopoietic Stem Cell Transplants

For years, cancer easily outpaced scientific progress. However, we are finally pulling even with blood cancers. Every 3 minutes, a diagnosis of blood cancer changes a life forever; every 9 minutes, a life is lost to the disease. This may seem bleak, but there is hope: hematopoietic stem cell transplants can cure blood cancers and multiple nonmalignant diseases.[1] For a sense of scale, there are more than 1 million people here in the United States living with, or in remission from, lymphoma, myeloma, or leukemia.

Hematopoietic progenitor cells (HPCs) are known as the "parent" cells from which all other blood cells develop. HPCs are found in blood and bone marrow, but these cells are often too damaged from chemo and radiation or they continue to manifest the underlying disease.[2] HPC transplants are used to replace or rebuild a patient's hematopoietic system. Patients who undergo HPC transplants may also experience graft-versus-tumor effect, eliminating residual disease. Put simply, HPC transplants often function as the only therapy with curative intent for patients with 1 of the more than 70 kinds of blood cancers and other blood disorders (such as leukemia, lymphoma, and myelodysplastic dysplasia), and they are becoming increasingly successful with each passing year.

Of the many reasons for improved outcomes with HPC transplantation, better matching of recipient to donor has had significant impact. Only 30% of patients have a perfect match among their siblings; in the past, the best outcomes for others were managed through transplant using an unrelated adult donor or with umbilical cord blood. With the growth of the world's adult donor registries to nearly 30 million individuals, many more patients have been able to find an acceptable unrelated donor. On this front, sheer altruism has helped turn the tide against cancer. Additionally, with advances to control graft-versus-host disease in settings in which human leukocyte antigens (HLAs) are less than perfectly matched between donor and recipient, the use of half-matched family members (haploidentical transplants) is improving access for thousands of patients who otherwise might not be eligible for curative therapy.[3]

It's worth expanding on this point. Just 3 decades ago, Congress created a predecessor to the C.W. "Bill" Young Cell Transplantation Program in order to establish a national registry of adult volunteer donors and of publicly available cord blood units. During this period, our nation's Be The Match Registry ballooned to more than 16 million adult volunteer marrow donors and 238,000 cord blood units. After factoring in international relationships, the global donor base includes approximately 29 million potential marrow donors and 712,000 cord blood units. Numbers have translated to action. Be The Match facilitated nearly 6200 marrow and umbilical cord blood transplants in 2016, for a total of 80,000 transplants since 1987.[4]

The takeaway here is simple: it's no longer a lack of donors that prevents life-saving transplantations. On the contrary, factors like the flawed federal payment policies are what now most directly limit America's transplantation infrastructure. While this is discouraging, some CMS policymakers have ignited the engine of reform in the outpatient setting,[5] according to the most recent Hospital Outpatient Prospective Payment System (HOPPS) rule. More importantly, it takes the action of only a few decision makers in Washington to push forward even more meaningful change.

CHELL

Jeffrey W. Chell, MD, is chief executive officer, National Marrow Donor Program.

The Intersection of Care and Medicare

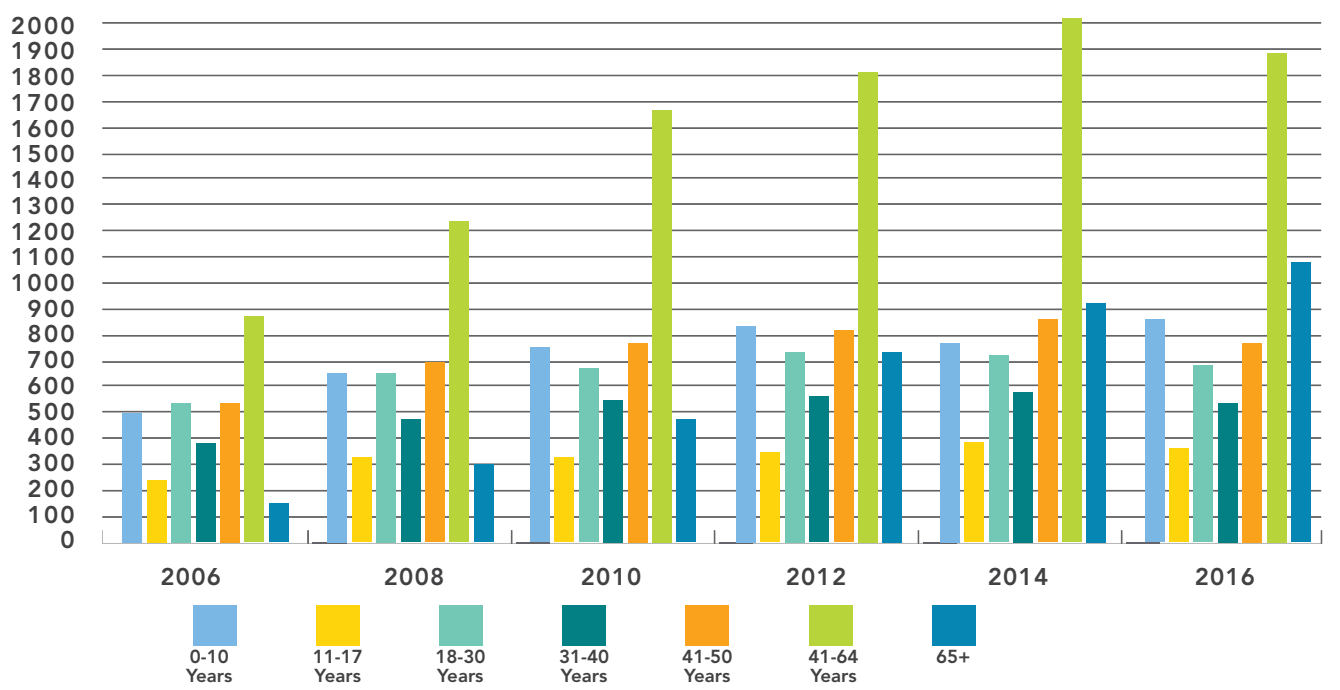
In order to understand the problem at hand, it's important to delve into the intricacies of Medicare payment policy. Every year, CMS puts forth a HOPPS rule as well as a Medicare Inpatient Prospective Payment System (IPPS) rule. As can be expected, the HOPPS rule pertains to procedures performed on patients who do not require hospital admission, while the IPPS rule applies to patients who require prolonged monitoring.

For years, both the HOPPS and the IPPS rules reimbursed significantly below the cost of HPC transplantation. In the outpatient setting, for example, the federal reimbursement rate was a stunning 47% below the procedure's true cost.[6] This shortfall manifested itself, in part, because CMS' payment formulae did not account for the cost of the marrow or cord blood acquisition. These procurement costs are anything but insignificant: the cost of locating and transporting HPCs to a patient in need frequently exceeds $45,000. As a result, many hospitals performing bone marrow transplants for Medicare patients regularly report losing tens of thousands of dollars on each case. Unsurprisingly, this triggered significant access issues, as both outpatient and inpatient facilities were hemorrhaging funds.

Logically, the chasm between Medicare reimbursement rates and the actual cost of care does not make much sense. So why is such a strategy in place? Although there is no overt explanation, it is very likely that federal policymakers—especially those who originally drafted the IPPS and HOPPS rules—did not anticipate that individuals over 65 years would benefit from marrow and stem cell transplants, as pretransplant treatment regimens were poorly tolerated by older patients with comorbid disease. Before 2000, »

MANY HOSPITALS PERFORMING BONE MARROW TRANSPLANTS FOR MEDICARE PATIENTS REGULARLY REPORT LOSING TENS OF THOUSANDS OF DOLLARS ON EACH CASE.

FIGURE 1. Number of Transplants by Age Between 2006 and 2016



Source: National Marrow Donor Program/Be The Match Fiscal Year 2016

many transplant programs considered being older than 50 years as a contraindication for a transplant from an unrelated donor. While this may have been appropriate years ago, today, the median age of diagnosis for acute myeloid leukemia, one of the most prominent blood cancers, is 67 years, according to the National Cancer Institute.[7] Moreover, Medicare beneficiaries are the most rapidly growing age segment for transplantation, receiving nearly 1100 procedures in 2015 alone (**Figure 1**). Most importantly, however, the shift toward an older demographic has arisen alongside improved clinical outcomes. HPC transplants are saving lives for those over 65 years, delivering hope where hope had not previously existed.

For these very reasons, the vast majority of private insurers cover 100% of the expenses for patients over 65 years who need HPC transplants. To veterans of health policy, this scenario will seem backwards. Typically, the government bears the burden of expensive, yet necessary, procedures while private payers drag their feet. However, when it comes to life-saving marrow and stem cell transplants, it has been the exact opposite. That's right: The government agency most responsible for the health and well-being of the American people has, for years, looked the other way.

MEDICARE BENEFICIARIES ARE THE MOST RAPIDLY GROWING AGE SEGMENT FOR TRANSPLANTATION, RECEIVING NEARLY 1100 PROCEDURES IN 2015 ALONE.

Rewriting HOPPS for the Better

Fortunately, the CMS/HHS team responsible for HOPPS finally took notice, and on November 1, 2016, CMS laid out its final HOPPS rule that would increase reimbursement to address the current inadequate rates that did not cover outpatient treatment costs, including the cost of acquiring bone marrow and cord blood for transplant.

The new rule contains significant changes to the payment amount and methodology for reporting costs related to bone marrow and cord blood transplants, which limits the use of the outpatient setting for transplant due to the significant underpayment under the current methodology. Key aspects of the rule include:

1. Outpatient hematopoietic cell transplantation (HCT; Current Procedural Terminology code 38240) will be moved into a new Comprehensive Ambulatory Payment Classification (C-APC). This allows all of the costs submitted on an outpatient HCT claim to remain together and be averaged with other outpatient HCT claims versus being diluted by other lower-cost services in a broader, noncomprehensive APC.

2. Payment for the new C-APC is proposed to be $27,752. This is a significant increase from the 2016 rate of $3015 and the proposed rate of $15,267. Although this still does not reflect the total acquisition costs associated with unrelated allogeneic transplant, let alone other costs incurred as part of the outpatient procedure, the new C-APC methodology will allow for upward adjustment based on cost reporting practices.

3. CMS has finalized a new cost center line for tracking donor procurement and related charges: new standard cost center 77, "Allogeneic Stem Cell Acquisition." Currently, donor-related costs are within a more general revenue code, which was subject to a cost:charge ratio edit based upon broader blood products data. By having a dedicated revenue code, CMS will have a clearer understanding of these costs and will better adjust rates in the future. This will apply only to allogeneic HCT. »

EFFECTIVE JANUARY 1, 2017

PERMANENT J-CODE J9352 NOW AVAILABLE FOR YONDELIS® (trabectedin)

Effective on January 1, 2017, YONDELIS® may be reported using the permanent J-Code **J9352 (Injection, trabectedin, 0.1 mg)**.[1]

- J9352 replaces J9999 (Not otherwise classified antineoplastic agent) and C9480 (Injection, trabectedin, 0.1 mg), previously used to report YONDELIS® on claims.[1,2] It also requires billing in units consistent with the new code's descriptor.*
- J9352 applies to most commercial and Medicare patients in both hospital outpatient and physician's office settings.

Please note, the fact that a drug, device, procedure, or service is assigned an HCPCS code and a payment rate does not imply coverage by the Medicare program. An HCPCS code and a payment rate indicate only how the product, procedure, or service may be paid if covered by the program. Fiscal Intermediaries/Medicare Administrative Contractors determine whether a drug, device, procedure, or other service meets all program requirements for coverage.[3]

Please see Important Safety Information on reverse side. Please see full Prescribing Information for YONDELIS® (trabectedin) available from your sales representative.

The information provided represents no statement, promise, or guarantee of Janssen Biotech, Inc., concerning levels of reimbursement, payment, or charge. Please consult your payer organization with regard to local or actual coverage, reimbursement policies, and determination processes. Information is subject to change without notice. Nothing herein may be construed as an endorsement, approval, recommendation, representation, or warranty of any kind by any plan or insurer referenced herein. This communication is solely the responsibility of Janssen Biotech, Inc.

Information is valid as of November 22, 2016, and is subject to change.

* Please check with individual payers and carriers for specific documentation and guidance when billing for a new drug.

1. Medicare Program: Hospital Outpatient Prospective Payment and Ambulatory Surgical Center Payment Systems and Quality Reporting Programs; Office of the Federal Register. https://www.federalregister.gov/documents/2016/11/14/2016-26515/medicare-program-hospital-outpatient-prospective-payment-and-ambulatory-surgical-center-payment. Published November 14, 2016. Accessed November 22, 2016.
2. YONDELIS® Reimbursement and Access Guide. Published August 2015.
3. Medicare National Coverage Determinations Manual. Centers for Medicare & Medicaid Services (CMS); May 16, 2016.

Yondelis® (trabectedin)

INDICATION

YONDELIS® (trabectedin) is indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS — YONDELIS® (trabectedin) is contraindicated in patients with known severe hypersensitivity, including anaphylaxis, to trabectedin.

WARNINGS AND PRECAUTIONS

Neutropenic sepsis, including fatal cases, can occur. In Trial 1, the incidence of Grade 3 or 4 neutropenia, based on laboratory values, was 43% (161/378). Median time to the first occurrence of Grade 3 or 4 neutropenia was 16 days (range: 8 days to 9.7 months). Median time to complete resolution of neutropenia was 13 days (range: 3 days to 2.3 months). Febrile neutropenia (fever ≥38.5°C with Grade 3 or 4 neutropenia) occurred in 18 patients (5%). Ten patients (2.6%) experienced neutropenic sepsis, 5 of whom had febrile neutropenia, which was fatal in 4 patients (1.1%). Assess neutrophil count prior to administration of each dose of YONDELIS® and periodically throughout the treatment cycle. Withhold YONDELIS® for neutrophil counts of less than 1500 cells/microliter on the day of dosing. Permanently reduce the dose of YONDELIS® for life-threatening or prolonged, severe neutropenia in the preceding cycle.

Rhabdomyolysis — YONDELIS® can cause rhabdomyolysis and musculoskeletal toxicity. In Trial 1, rhabdomyolysis leading to death occurred in 3 (0.8%) of the 378 patients. Elevations in creatine phosphokinase (CPK) occurred in 122 (32%) of the 378 patients receiving YONDELIS®, including Grade 3 or 4 CPK elevation in 24 patients (6%), compared to 15 (9%) of the 172 patients receiving dacarbazine with any CPK elevation, including 1 patient (0.6%) with Grade 3 CPK elevation. Among the 24 patients receiving YONDELIS® with Grade 3 or 4 CPK elevation, renal failure occurred in 11 patients (2.9%); rhabdomyolysis with the complication of renal failure occurred in 4 of these 11 patients (1.1%). Median time to first occurrence of Grade 3 or 4 CPK elevations was 2 months (range: 1 to 11.5 months). Median time to complete resolution was 14 days (range: 5 days to 1 month). Assess CPK levels prior to each administration of YONDELIS®. Withhold YONDELIS® for serum CPK levels more than 2.5 times the upper limit of normal. Permanently discontinue YONDELIS® for rhabdomyolysis.

Hepatotoxicity, including hepatic failure, can occur. Patients with serum bilirubin levels above the upper limit of normal or AST or ALT levels >2.5 x ULN were not enrolled in Trial 1. In Trial 1, the incidence of Grade 3-4 elevated liver function tests (defined as elevations in ALT, AST, total bilirubin, or alkaline phosphatase) was 35% (134/378). Median time to development of Grade 3-4 elevation in ALT or AST was 29 days (range: 3 days to 11.5 months). Of the 134 patients with Grade 3 to 4 elevations in LFTs, 114 (85%) experienced complete resolution with the median time to complete resolution of 13 days (range: 4 days to 4.4 months). In Trial 1, the incidence of drug-induced liver injury (defined as concurrent elevation in ALT or AST of more than three times the upper limit of normal, alkaline phosphatase less than two times the upper limit of normal, and total bilirubin at least two times the upper limit of normal) was 1.3% (5/378). ALT or AST elevation greater than eight times the ULN occurred in 18% (67/378) of patients. Assess LFTs prior to each administration of YONDELIS® and as clinically indicated based on underlying severity of pre-existing hepatic impairment. Manage elevated LFTs with treatment interruption, dose reduction, or permanent discontinuation based on severity and duration of LFT abnormality.

Cardiomyopathy, including cardiac failure, congestive heart failure, ejection fraction decreased, diastolic dysfunction, or right ventricular dysfunction can occur. In Trial 1, patients with a history of New York Heart Association Class II to IV heart failure or abnormal left ventricular ejection fraction (LVEF) at baseline were ineligible. In Trial 1, cardiomyopathy occurred in 23 patients (6%) receiving YONDELIS® and in four patients (2.3%) receiving dacarbazine. Grade 3 or 4 cardiomyopathy occurred in 15 patients (4%) receiving YONDELIS® and 2 patients (1.2%) receiving dacarbazine; cardiomyopathy leading to death occurred in 1 patient (0.3%) receiving YONDELIS® and in none of the patients receiving dacarbazine. The median time to development of Grade 3 or 4 cardiomyopathy in patients receiving YONDELIS® was 5.3 months (range: 26 days to 15.3 months). Assess left ventricular ejection fraction (LVEF) by echocardiogram or multigated acquisition (MUGA) scan before initiation of YONDELIS® and at 2- to 3-month intervals thereafter until YONDELIS® is discontinued. Withhold YONDELIS® for LVEF below lower limit of normal. Permanently discontinue YONDELIS® for symptomatic cardiomyopathy or persistent left ventricular dysfunction that does not recover to lower limit of normal within 3 weeks.

Extravasation Resulting in Tissue Necrosis — Extravasation of YONDELIS®, resulting in tissue necrosis requiring debridement, can occur. Evidence of tissue necrosis can occur more than 1 week after the extravasation. There is no specific antidote for extravasation of YONDELIS®. Administer YONDELIS® through a central venous line.

Embryofetal Toxicity — Based on its mechanism of action, YONDELIS® can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during therapy and for at least 2 months after the last dose of YONDELIS®. Advise males with female partners of reproductive potential to use effective contraception during therapy and for at least 5 months after the last dose of YONDELIS®.

Adverse Reactions — The most common (≥20%) adverse reactions are nausea (75%), fatigue (69%), vomiting (46%), constipation (37%), decreased appetite (37%), diarrhea (35%), peripheral edema (28%), dyspnea (25%), and headache (25%).

The most common (≥5%) grades 3-4 laboratory abnormalities are: neutropenia (43%), increased ALT (31%), thrombocytopenia (21%), anemia (19%), increased AST (17%), and increased creatine phosphokinase (6.4%).

DRUG INTERACTIONS

Effect of Cytochrome CYP3A Inhibitors — Avoid using strong CYP3A inhibitors (e.g., oral ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, indinavir, lopinavir, ritonavir, boceprevir, nelfinavir, saquinavir, telaprevir, nefazodone, conivaptan) in patients taking YONDELIS®. Avoid taking grapefruit or grapefruit juice. If a strong CYP3A inhibitor for short-term use (i.e., less than 14 days) must be used, administer the strong CYP3A inhibitor 1 week after the YONDELIS® infusion, and discontinue it the day prior to the next YONDELIS® infusion.

Effect of Cytochrome CYP3A Inducers — Avoid using strong CYP3A inducers (e.g., rifampin, phenobarbital, St. John's wort) in patients taking YONDELIS®.

Please see full Prescribing Information for YONDELIS® (trabectedin) available from your sales representative.

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Janssen Oncology
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Pharma Mar

Yondelis® (trabectedin)

 2/17 066465-170201

YONDELIS (trabectedin) for injection, for intravenous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

YONDELIS® is indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen *[see Clinical Studies (14) in Full Prescribing Information]*.

CONTRAINDICATIONS

YONDELIS is contraindicated in patients with known severe hypersensitivity, including anaphylaxis, to trabectedin.

WARNINGS AND PRECAUTIONS

Neutropenic Sepsis: Neutropenic sepsis, including fatal cases, can occur with YONDELIS. In Trial 1, the incidence of Grade 3 or 4 neutropenia, based on laboratory values, in patients receiving YONDELIS was 43% (161/378). The median time to the first occurrence of Grade 3 or 4 neutropenia was 16 days (range: 8 days to 9.7 months); the median time to complete resolution of neutropenia was 13 days (range: 3 days to 2.3 months). Febrile neutropenia (fever ≥38.5°C with Grade 3 or 4 neutropenia) occurred in 18 patients (5%) treated with YONDELIS. Ten patients (2.6%) experienced neutropenic sepsis, 5 of whom had febrile neutropenia, which was fatal in 4 patients (1.1%).

Assess neutrophil count prior to administration of each dose of YONDELIS and periodically throughout the treatment cycle. Withhold YONDELIS for neutrophil counts of less than 1,500 cells/microliter on the day of dosing. Permanently reduce the dose of YONDELIS for life-threatening or prolonged, severe neutropenia in the preceding cycle *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

Rhabdomyolysis: YONDELIS can cause rhabdomyolysis and musculoskeletal toxicity. In Trial 1, rhabdomyolysis leading to death occurred in 3 (0.8%) of the 378 patients receiving YONDELIS. Elevations in creatine phosphokinase (CPK) occurred in 122 (32%) of the 378 patients receiving YONDELIS, including Grade 3 or 4 CPK elevation in 24 patients (6%), compared to 15 (9%) of the 172 patients receiving dacarbazine with any CPK elevation, including 1 patient (0.6%) with Grade 3 CPK elevation. Among the 24 patients receiving YONDELIS with Grade 3 or 4 CPK elevation, renal failure occurred in 11 patients (2.9%); rhabdomyolysis with the complication of renal failure occurred in 4 of these 11 patients (1.1%). The median time to first occurrence of Grade 3 or 4 CPK elevations was 2 months (range: 1 to 11.5 months). The median time to complete resolution was 14 days (range: 5 days to 1 month).

Assess CPK levels prior to each administration of YONDELIS. Withhold YONDELIS for serum CPK levels more than 2.5 times the upper limit of normal. Permanently discontinue YONDELIS for rhabdomyolysis *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

Hepatotoxicity: Hepatotoxicity, including hepatic failure, can occur with YONDELIS. Patients with serum bilirubin levels above the upper limit of normal or AST or ALT levels >2.5 x upper limit of normal were not enrolled in Trial 1. In Trial 1, the incidence of Grade 3-4 elevated liver function tests (LFTs; defined as elevations in ALT, AST, total bilirubin, or alkaline phosphatase) was 35% (134/378) in patients receiving YONDELIS. The median time to development of Grade 3-4 elevation in ALT or AST was 29 days (range: 3 days to 11.5 months). Of the 134 patients with Grade 3-4 elevations in LFTs, 114 (85%) experienced complete resolution with the median time to complete resolution of 13 days (range: 4 days to 4.4 months).

In Trial 1, the incidence of drug-induced liver injury (defined as concurrent elevation in ALT or AST of more than three times the upper limit of normal, alkaline phosphatase less than two times the upper limit of normal, and total bilirubin at least two times the upper limit of normal) was 1.3% (5/378) in patients receiving YONDELIS. ALT or AST elevation greater than eight times the upper limit of normal occurred in 18% (67/378) of patients receiving YONDELIS.

Assess LFTs prior to each administration of YONDELIS and as clinically indicated based on underlying severity of pre-existing hepatic impairment. Manage elevated LFTs with treatment interruption, dose reduction, or permanent discontinuation based on severity and duration of LFT abnormality *[see Dosage and Administration (2.3) in Full Prescribing Information and Use in Specific Populations]*.

Cardiomyopathy: Cardiomyopathy including cardiac failure, congestive heart failure, ejection fraction decreased, diastolic dysfunction, or right ventricular dysfunction can occur with YONDELIS. In Trial 1, patients with a history of New York Heart Association Class II to IV heart failure or abnormal left ventricular ejection fraction (LVEF) at baseline were ineligible. In Trial 1, cardiomyopathy occurred in 23 patients (6%) receiving YONDELIS and in four patients (2.3%) receiving dacarbazine. Grade 3 or 4 cardiomyopathy occurred in 15 patients (4%) receiving YONDELIS and 2 patients (1.2%) receiving dacarbazine; cardiomyopathy leading to death occurred in 1 patient (0.3%) receiving YONDELIS and in none of the patients receiving dacarbazine. The median time to development of Grade 3 or 4 cardiomyopathy in patients receiving YONDELIS was 5.3 months (range: 26 days to 15.3 months).

Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of YONDELIS and at 2- to 3-month intervals thereafter until YONDELIS is discontinued. Withhold YONDELIS for LVEF below lower limit of normal. Permanently discontinue YONDELIS for symptomatic cardiomyopathy or persistent left ventricular dysfunction that does not recover to lower limit of normal within 3 weeks *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

Extravasation Resulting in Tissue Necrosis: Extravasation of YONDELIS, resulting in tissue necrosis requiring debridement, can occur. Evidence of tissue necrosis can occur more than 1 week after the extravasation. There is no specific antidote for extravasation of YONDELIS. Administer YONDELIS through a central venous line *[see Dosage and Administration (2.5) in Full Prescribing Information]*.

Embryofetal Toxicity: Based on its mechanism of action, YONDELIS can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during therapy and for at least 2 months after the last dose of YONDELIS. Advise males with female partners of reproductive potential to use effective contraception during therapy and for at least 5 months after the last dose of YONDELIS *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling: • Anaphylaxis *[see Contraindications]* • Neutropenic Sepsis *[see Warnings and Precautions]* • Rhabdomyolysis *[see Warnings and Precautions]* • Hepatotoxicity *[see Warnings and Precautions]* • Cardiomyopathy *[see Warnings and Precautions]* • Extravasation Resulting in Tissue Necrosis *[see Warnings and Precautions]*

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

The data described below reflect exposure to YONDELIS in 755 patients with soft tissue sarcoma including 197 (26%) patients exposed to YONDELIS for greater than or equal to 6 months and 57 (8%) patients exposed to YONDELIS for greater than or equal to 1 year. The safety of YONDELIS was evaluated in six open-label, single-arm trials, in which 377 patients received YONDELIS and one open-label, randomized, active-controlled clinical trial in which 378 patients received YONDELIS (Trial 1). All patients received YONDELIS at the recommended dosing regimen of 1.5 mg/m² administered as an intravenous infusion over 24 hours once every 3 weeks (q3wk, 24-h). The median age was 54 years (range: 18 to 81 years), 63% were female, and all patients had metastatic soft tissue sarcoma.

Tables 1 and 2 present selected adverse reactions and laboratory abnormalities, respectively, observed in Trial 1, an open-label, randomized (2:1), active-controlled trial in which 550 patients with previously treated leiomyosarcoma or liposarcoma (dedifferentiated, myxoid round cell, or pleomorphic) received YONDELIS 1.5 mg/m² intravenous infusion over 24 hours once every 3 weeks (n=378) or dacarbazine 1000 mg/m² intravenous infusion over 20 to 120 minutes once every 3 weeks (n=172) *[see Clinical Studies (14) in Full Prescribing Information]*. All patients treated with YONDELIS were required to receive dexamethasone 20 mg intravenous injection 30 minutes prior to start of the YONDELIS infusion.

In Trial 1, patients had been previously treated with an anthracycline- and ifosfamide-containing regimen or with an anthracycline-containing regimen and one additional cytotoxic chemotherapy regimen. The trial excluded patients with known central nervous system metastasis, elevated serum bilirubin or significant chronic liver disease, such as cirrhosis or active hepatitis, and history of myocardial infarction within 6 months, history of New York Heart Association Class II to IV heart failure, or abnormal left ventricular ejection fraction at baseline. The median age of patients in Trial 1 was 57 years (range: 17 to 81 years), with 69% female, 77% White, 12% Black or African American, 4% Asian, and <1% American Indian or Alaska Native. The median duration of exposure to trabectedin was 13 weeks (range: 1 to 127 weeks) with 30% of patients exposed to YONDELIS for greater than 6 months and 7% of patients exposed to YONDELIS for greater than 1 year.

In Trial 1, adverse reactions resulting in permanent discontinuation of YONDELIS occurred in 26% (98/378) of patients; the most common were increased liver tests (defined as ALT, AST, alkaline phosphatase, bilirubin) (5.6%), thrombocytopenia (3.4%), fatigue (1.6%), increased creatine phosphokinase (1.1%), and decreased ejection fraction (1.1%). Adverse reactions that led to dose reductions occurred in 42% (158/378) of patients treated with YONDELIS; the most common were increased liver tests (24%), neutropenia (including febrile neutropenia) (8%), thrombocytopenia (4.2%), fatigue (3.7%), increased creatine phosphokinase (2.4%), nausea (1.1%), and vomiting (1.1%). Adverse reactions led to dose interruptions in 52% (198/378) of patients treated with YONDELIS; the most common were neutropenia (31%), thrombocytopenia (15%), increased liver tests (6%), fatigue (2.9%), anemia (2.6%), increased creatinine (1.1%), and nausea (1.1%).

The most common adverse reactions (>20%) were nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, and headache. The most common laboratory abnormalities (>20%) were increases in AST or ALT, increased alkaline phosphatase, hypoalbuminemia, increased creatinine, increased creatine phosphokinase, anemia, neutropenia, and thrombocytopenia.

Table 1: Selected Adverse Reactions[a] Occurring in ≥10% of Patients Receiving YONDELIS and at a Higher Incidence than in the Control Arm - Trial 1

System Organ Class Adverse Reaction	YONDELIS (N=378)		Dacarbazine (N=172)	
	All Grades[b] (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal disorders				
Nausea	75	7	50	1.7
Vomiting	46	6	22	1.2
Constipation	37	0.8	31	0.6
Diarrhea	35	1.6	23	0
General disorders and administration site conditions				
Fatigue[c]	69	8	52	1.7
Peripheral edema	28	0.8	13	0.6
Metabolism and nutrition disorders				
Decreased appetite	37	1.9	21	0.6
Respiratory, thoracic and mediastinal disorders				
Dyspnea	25	4.2	20	1.2
Nervous system disorders				
Headache	25	0.3	19	0
Musculoskeletal and connective tissue disorders				
Arthralgia	15	0	8	1.2
Myalgia	12	0	6	0
Psychiatric disorders				
Insomnia	15	0.3	9	0

[a] Limited to adverse reactions at a rate of ≥10% in the trabectedin arm and at a rate higher in the trabectedin arm compared with dacarbazine arm by ≥5% in overall incidence or by ≥2% for Grade 3-4 adverse reactions.
[b] Toxicity grade is based on NCI common toxicity criteria, version 4.0.
[c] Fatigue is a composite of the following adverse event terms: fatigue, asthenia, and malaise.

Other clinically important adverse reactions observed in <10% of patients (N=755) with soft tissue sarcoma receiving YONDELIS were:

Nervous system disorders: peripheral neuropathy, paresthesia, hypoesthesia.

Respiratory, thoracic, and mediastinal disorders: pulmonary embolism.

Table 2: Incidence of Selected Treatment-Emergent Laboratory Abnormalities[a] - Trial 1

Laboratory Abnormalities	YONDELIS		Dacarbazine	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Increased ALT	90	31	33	0.6
Increased AST	84	17	32	1.2
Increased alkaline phosphatase	70	1.6	60	0.6
Hypoalbuminemia	63	3.7	51	3.0
Increased creatinine	46	4.2	29	1.2
Increased creatine phosphokinase	33	6.4	9	0.6
Hyperbilirubinemia	13	1.9	5	0.6
Hematology				
Anemia	96	19	79	12
Neutropenia	66	43	47	26
Thrombocytopenia	59	21	57	20

[a] Treatment-emergent laboratory abnormalities including those higher in the trabectedin arm compared with the dacarbazine arm by ≥5% (all Grades) or by ≥2% (Grade 3-4). Incidence based on number of patients who had both baseline and at least one on-study laboratory measurement.
YONDELIS group (range: 373 to 377 patients) and dacarbazine group (range: 166 to 168 patients).

DRUG INTERACTIONS

Effect of Cytochrome CYP3A Inhibitors: Coadministration of YONDELIS with ketoconazole, a strong CYP3A inhibitor, increased systemic exposure of trabectedin by 66%. Avoid using strong CYP3A inhibitors (e.g., oral ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, indinavir, lopinavir, ritonavir, boceprevir, nelfinavir, saquinavir, telaprevir, nefazodone, conivaptan) in patients taking YONDELIS. Avoid taking grapefruit or grapefruit juice during YONDELIS treatment. If a strong CYP3A inhibitor for short-term use (i.e., less than 14 days) must be used, administer the strong CYP3A inhibitor 1 week after the YONDELIS infusion, and discontinue it the day prior to the next YONDELIS infusion *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

(continued from SP174)

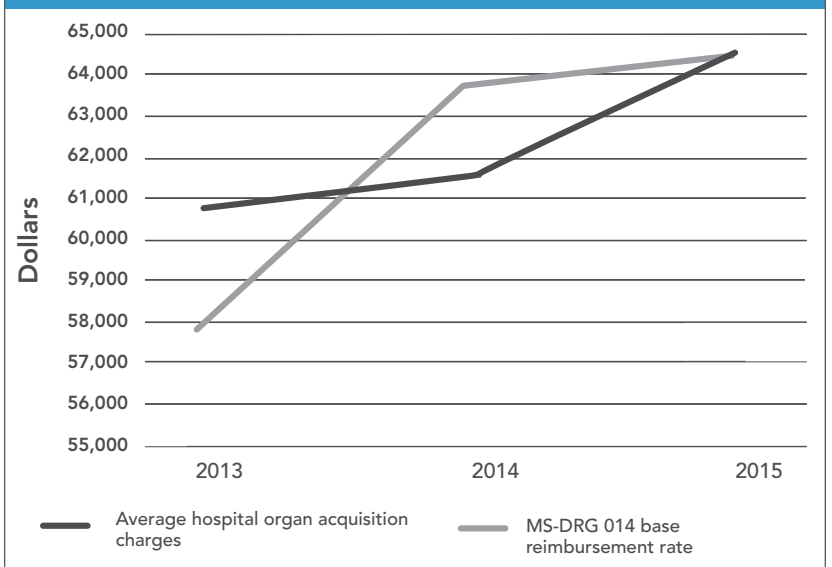
4. Acquisition charges, including National Bone Marrow Donor Program fees and costs of HLA typing, donor evaluation, and collection of cells, among other costs, will be specifically required to be reported in Field 42 on CMS Form 1450 (UB-04) so that CMS may assess the charges and gauge how well the C-APC payment reflects the costs of providing these services.

While there remains room for improvement in the reimbursement rate to pay for cell acquisition costs, for which transplant centers are currently under reimbursed, the new methodology is unquestionably a step in the right direction. However, 1 major problem is that most transplants do not occur in outpatient facilities; rather, the vast majority of HPC procedures take place in the inpatient setting. Further, a lack of coordination between federal policymakers dealing with HOPPS and IPPS has prevented government efforts to harmonize standards. Therefore, precarious payment and access issues continue to persist.

Inaction for Inpatients

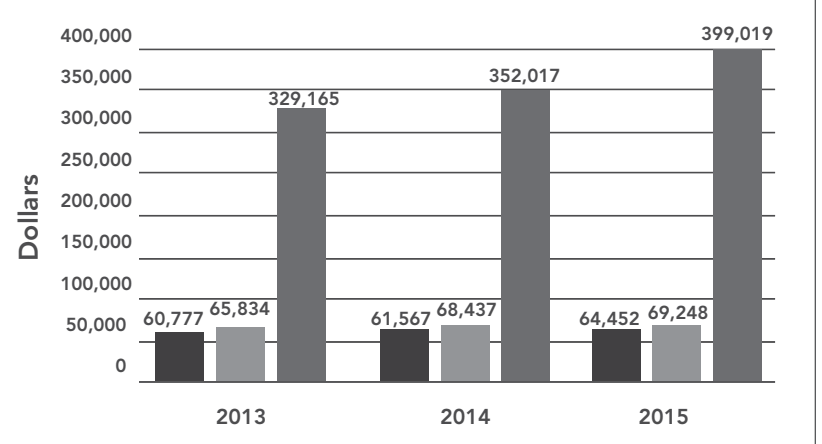
Not only do 90% of all HPC transplants take place in the inpatient setting, but the reimbursement deficits exceed those of outpatient facilities. On this front, the numbers are notable. As illustrated in **Figure 2**, the Medicare base reimbursement rate was surpassed by average hospital organ acquisition

FIGURE 2. Difference Between Hospital Acquisition Charges and Reimbursement Rate



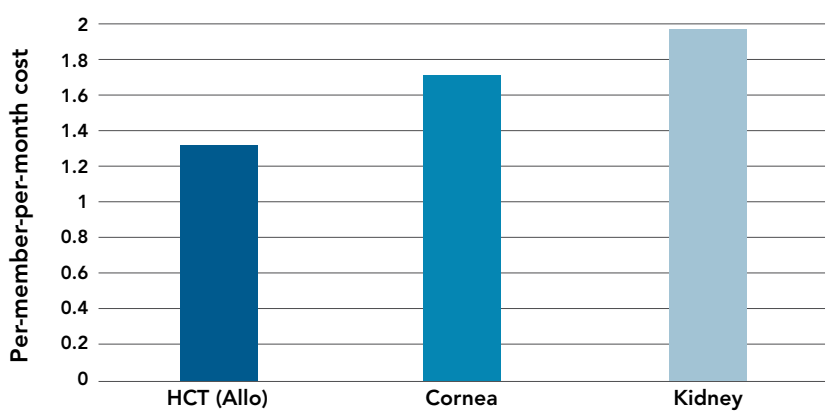
MS-DRG indicates Medicare Severity Diagnosis Related Group.

FIGURE 3. Total Charges for HCT and Donor Search versus Reimbursement



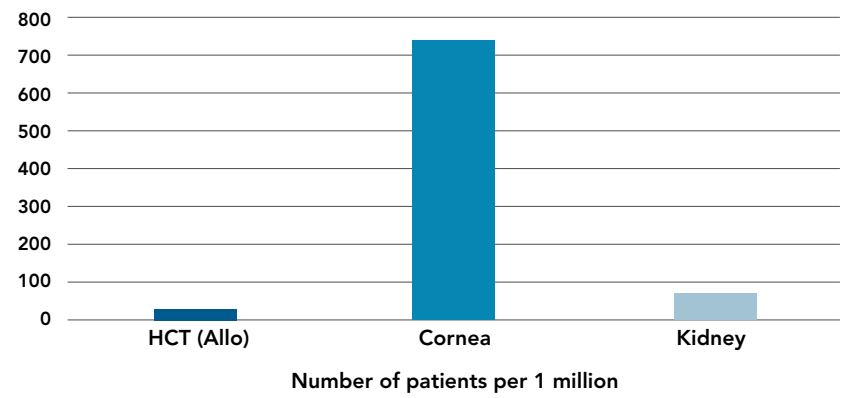
DRG indicates diagnosis-related group; HCT, hematopoietic cell transplant.

FIGURE 4. Per-Member Per-Month Cost of Transplants for Patients 65 Years and Older



HCT (Allo) indicates allogeneic hematopoietic cell transplantation.

FIGURE 5. Estimated Number of Patients 65 Years and Older Accessing Transplants



HCT (Allo) indicates allogeneic hematopoietic cell transplantation.

charges in 2015,[8] which means that Medicare has not historically paid enough to cover the costs of procurement. Hence, each additional dollar that the hospital must bill for the transplantation itself contributes to a net loss. Cost-reimbursement deviations are even greater at the state level. In Georgia, for instance, hospitals performing cord blood transplants are already $10,652 in the hole even before admitting a patient. This number is higher in places like Rhode Island, where inpatient facilities are $21,540 in the red before treatment begins. Still, this begs the question: how much does a transplant typically cost?

The actual scale of unreimbursed expenses is significant. As illustrated in **Figure 3**, the average reported hospital charge for an HPC transplant in 2015 was $399,019, while the Medicare Severity Diagnosis Related Group (DRG) 14 base reimbursement was $64,452—a difference of $334,567.[8] Those managing hospital finances would rightfully scoff at such an imbalance. Despite being potentially detrimental for patient access, many medical facilities are understandably assessing the sustainability of performing future transplants. Such uncertainty, however, could be eliminated via common-sense, comprehensive action, as was done with HOPPS.

Addressing IPPS Underfunding

CMS officials managing the inpatient payments can implement 2 policy solutions:

- Rewrite the IPPS rule to raise the base Medicare reimbursement rate, which is fairly straightforward. In the outpatient setting, policymakers lifted reimbursement rates by a factor of 9 in 2016 alone. Hence, there is every reason to believe that such convincing action can be mirrored.
- There is also a strategic workaround available to those in Washington: to reimburse cellular transplants in the same manner as solid organs (eg, kidneys). Under current regulations, Medicare provides a type of pass-through for acquisition costs, reimbursing hospitals for these costs separate from the IPPS rate. In this way, the government guarantees that hospitals will be adequately compensated for acquisition expenses and that such expenses do not create a disincentive for providing transplants to older patients. Implementing a policy similar to that for living kidney donors would not entail a massive overhaul of federal policies, but simply recognizing the acquisition costs apart from the DRG, as is done with solid organs. The solution makes sense on multiple levels, as it would create parity across Medicare transplant policies and reduce the role of cost in limiting access for beneficiaries.

Moreover, such a policy would have a positive impact on patients, while making an insignificant dent in Medicare spending. As shown in **Figures 4** and **5**, HCTs cost less than both cornea and kidney transplants and they are needed by fewer patients.[9] Therefore, it just makes sense for CMS to reimburse hospitals for their cell acquisition cost separate from the DRG rate, just as they do for the acquisition cost of solid organs.

In the end, the future is brighter than ever before for patients suffering from blood cancers. Technology is progressing rapidly, medical treatments are tackling diseases that were death sentences just decades ago, and policymaking is finally beginning to catch up with this progress. We now need CMS to take the next logical step and create standardized, fair reimbursement rules for all Medicare beneficiaries, no matter where they choose to receive care. As a physician and an advocate, I will echo the same message I have delivered so often: the evidence is clear, and it is time for a change. It's what my patients and so many others deserve. ◆

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COST OF CARE

The Oncogenic Hepatitis C Virus and Direct-Acting Antivirals: Economic Implications for Hepatocellular Carcinoma in Medicaid Beneficiaries With Cirrhosis

S. Mantravadi, PhD, MS, MPH

ABSTRACT

BACKGROUND: The hepatitis C virus (HCV) is an oncogenic virus that is the primary risk factor for hepatocellular carcinoma (HCC), illustrating the relative importance of tertiary prevention of liver cancer.[1,2] Health disparities in HCV indicate its disproportionate prevalence among low-income populations. Due to low efficacy rates, predominant treatment regimens do not significantly prevent disease progression toward HCC among all populations—although the risk of HCV is higher in the Medicaid population. Direct-acting antivirals (DAAs) result in improved efficacy and ease of administration compared with current hepatitis treatment options.

METHODS: Published literature and the Medicaid National Average Drug Acquisition Cost were used to estimate treatment costs, and averted medical HCC costs were modeled for DAAs and prevailing treatment options for HCV.

RESULTS: Approximately $14,473 in medical expenses related to HCC treatment per person can be avoided over the next 10 years with the sofosbuvir-ledipasvir combination treatment for cirrhotic Medicaid beneficiaries infected with HCV genotype 1a. The DAAs result in lower HCC-related medical spending costs than peginterferon-ribavirin and watch-and-wait regimens.

CONCLUSIONS: The oncogenic effects of HCV can impact patient outcomes for HCC and have economic implications for medical spending. The study provides evidence that underscores the importance of treating patients early in the disease process to reap savings related to reduced risks of HCC.

Introduction

The hepatitis C virus (HCV) is an oncogenic virus that can lead to variable degrees of liver fibrosis and damage (cirrhosis). HCV and associated cirrhosis are the leading causes of hepatocellular carcinoma (HCC).[1,3] Most cases of HCC are HCV related; treatment of HCV can reduce the risk of HCC by 50%.[1] The risk of HCC increases by 2-6% annually.[4] The lag time between acute phase and the development of chronic HCV infection can be 20 to 30 years,[5] thus creating a silent epidemic of patients infected with HCV who are at risk for HCC.[6]

Several groups are at an increased risk for HCV. Disease prevalence is higher in the population under age 55, and it disproportionally affects the poor.[7,8] This places the Medicaid population at greater risk and makes the treatment of HCV a priority for Medicaid. The number of Medicaid beneficiaries with oncogenic HCV is high and is only rising.[9,10]

Reaching sustained virologic response (SVR) has been shown to reduce the imminent risk of HCC; however, the predominant treatment regimen for HCV has only had modest efficacy. Although treatment has been noted to delay development of HCV-related HCC,[2] the lack of ease of administration and the associated adverse effects result in high percentages of treatment discontinuation, thereby reducing the absolute effect of peginterferon-ribavirin treatment. A new form of treatment, direct-acting antivirals (DAAs), has emerged to overcome the notable limitations of interferon-based regimens. These medications are expensive, with treatment costs averaging $80,000 for a 12-week regimen, but they do have a much greater success rate over the established interferon-ribavirin regimen, especially for patients with cirrhosis and they reduce the potential risks for HCC. Due to the high prevalence of HCV in the under 55-years group and low-income populations, Medicaid programs are facing the economic burden of efficacious, yet expensive, DAA treatments for HCV.[11-15] The cost:benefit ratio of DAAs is being considered, particularly in the context of greater efficacy, reduced risk of HCC, averted HCC treatment–related expenses, and unnecessary future healthcare utilization.

THIS STUDY MODELED A COHORT OF MEDICAID ENROLLEES, INCLUDING BENEFICIARIES ACROSS ALL STATES, OVER A PERIOD OF 10 YEARS.

Patients with HCV and cirrhosis face several complications with liver and nonliver-related cancers therapies.[3] The prognosis and treatment decisions for HCC depend on the extent of fibrosis in the liver,[3] illustrating the importance of efficacious HCV treatments. The increased SVR rate/ "cure" associated with interferon-free DAA treatments lowers the need for HCV-related HCC treatments.[3] However, specific data on the number of cases and associated reduction in HCC costs with the use of DAAs have not been fully researched.

To evaluate changes and economic implications for HCC savings, this study modeled HCV-infected genotype 1a Medicaid beneficiaries with cirrhosis undergoing current FDA-approved and American Association for the Study of Liver Diseases (AASLD) and Infectious Disease Society of America (IDSA)–recommended treatments compared with the prevailing options of interferon-ribavirin regimen and watch-and-wait (no treatment for oncogenic disease) over a 10-year time span.

Methods

This study modeled a cohort of Medicaid enrollees, including beneficiaries across all states, over a period of 10 years. Published data and reports were used to define the size of the population of patients with Medicaid and HCV genotype 1a infection.[16,17] The 10-year time frame is ideal to determine both the short-term and long-term impact of these treatments. To qualify for Medicare, individuals must be 65 years; thus, the modeled cohort was limited to Medicaid beneficiaries 55 years and younger.[17] The model considered 28,765 patients with HCV with cirrhosis on Medicaid, as per public literature estimates, age/genotype distributes, and the chronic HCV cohort study.[10] This study was exempt from evaluation by an Institutional Review Board as only published literature and existing data were used.

Probabilities of disease progression, obtained from published literature, were included. In the first year, patients with HCV with cirrhosis received a specific treatment regimen (12-to-48 weeks, depending on the regimen) and patients who had not discontinued treatment could reach SVR/"cure" after their HCV treatment ends. The cohort of Medicaid beneficiaries was modeled year-

TABLE 1. Model Inputs

INPUT VALUE/VARIABLE	REFERENCES	BASE CASE VALUE (RANGE)
Rate Variable: Treatment Response Rate (SVR reached)		
No treatment [18,19]		1% (.7%-1.7%)
Peginterferon-ribavirin	Clinical trials: Pegasys, Pegintron, Copegus, Rebetol	10%
Elbasvir-grazoprevir, 12 weeks	Clinical trials: C-EDGE TN	92% (97%)
Sofosbuvir-ledipasvir, 12 weeks	Clinical trials: ION 1, double blind NEUTRINO, open label	97% (67%-99.9%); range: genotype 1 Treatment-naïve cirrhotic (ION 1), and genotype 1 cirrhotic (NEUTRINO) ION 1 (84.2%-99.9%) NEUTRINO (67%-89%)
Sofosbuvir-velpatasvir without ribavirin, 12 weeks	Clinical trials: ALLY-1	98% (95%-99%)
Treatment Discontinuation		
All direct-acting antivirals[20]		8.1% (0%-8.7%)
Peginterferon-ribavirin[21]		12.3% (0%-12.3%)
Transition Probabilities[a]		
F4 with SVR to decompensated cirrhosis[18]		.008
F4 without SVR to decompensated cirrhosis[18]		.039
F4 with SVR to liver cancer[18]		.005
F4 without SVR to liver cancer[18]		.014
Decompensated cirrhosis to liver cancer[18]		.068
Decompensated cirrhosis to liver transplant[18]		.023
Treatment Cost ($/day)		
Pegylated interferon-ribavirin	Medicaid National Average Drug Acquisition Cost	Pegylated interferon (Pegasys ProClick): 1685.5 (1264.15-2106.8); Ribavirin: 0.87 (0.66–1.1)
Elbasvir-grazoprevir[23]		Elbasvir-grazoprevir: 650 (487.5-812.5)
Sofosbuvir-ledipasvir 12 weeks	Medicaid National Average Drug Acquisition Cost	Sofosbuvir-ledipasvir: 1091.2 (818.4-1364.0)
Sofosbuvir-velpatasvir 12 weeks	Medicaid National Average Drug Acquisition Cost	Sofosbuvir-velpatasvir: 890 (667.5-1112.5)

SVR indicates sustained virologic response.
[a]Sensitivity analysis not conducted.

by-year, beginning in the second year, to evaluate changes in the number of patients who would progress to HCC, as well as HCC-related costs. The successive disease progression stages that were modeled were F4-compensated cirrhosis/fibrosis, decompensated cirrhosis (DCC), liver cancer, and liver transplantation.[18] During each successive year that the cohort was modeled, the patient progressed toward the endpoint along the disease stages, as per expected probabilities, unless a treatment-related "cure" was documented. At baseline, all patients were assumed to have compensated cirrhosis. If an individual failed to reach SVR/ "cure", he or she had a 1-time, 50% chance of retreatment with the same regimen (year 2). Each year, an individual might remain in the same disease stage or have disease progression (F4 compensated to DCC or liver cancer, DCC to liver cancer or transplant, liver cancer to transplant).[18]

For our study, we evaluated elbasvir-grazoprevir, sofosbuvir-ledipasvir, sofosbuvir-velpatasvir, and ribavirin-peginterferon, which are FDA-approved and AASLD-IDSA–recommended treatment regimens for treatment-naïve patients infected with HCV genotype 1a who have cirrhosis.[17] These medications were evaluated in the context of a watch-and-wait scenario.

For the treatment regimens considered, efficacy rates from published clinical trial data (NEUTRINO, ION-1, OPTIMIST-2, ALLY, and ASTRAL trials), treatment discontinuation rates from observational studies and meta analyses, and treatment costs from the Medicaid National Average Drug Acquisition Cost and published literature were used.[19-23] All-cause healthcare costs for HCV disease progression (F4, DCC, HCC, and liver transplantation) were extracted from published literature.[24] **Table 1** illustrates the variable inputs used in the model.

The number of patients who progressed to HCC from F4 cirrhosis, as well as their related costs, were tabulated annually. For each treatment, all-cause healthcare/medical costs for HCC that were averted by treatment and medical costs encountered for no treatment/watch-and-wait were accumulated over 10 years. In addition, the number of patients with HCV who progressed to HCC was determined.

Results

As expected, fewer patients who reached SVR developed HCC. In year 3, those who developed HCC with SVR peaked, as this depended on both the number of patients who reached SVR due to retreatment and the presence of patients who progressed to DCC in year 2. Fewer patients who reached SVR developed HCC compared with patients who were not "cured" and continued through disease progression—a key benefit of DAA treatment, as illustrated in **Table 2**.

In the first year (year 2) of follow-up after treatment, 1232 patients developed HCC. A peak in HCC cases that year was associated with a rise in patients with DCC. Further, an increased number of patients with cirrhosis progressed to DCC, one of the clinical precursors of HCC. Each year thereafter saw a decrease in the number of individuals who developed HCC.

In general, as shown in **Table 3**, of 28,765 patients with HCV who had cirrhosis, 12,887 developed HCC after treatment with sofosbuvir-veltapasvir over a period of 10 years, and peginterferon-ribavirin treatment resulted in approximately 15,000 patients with HCV who had cirrhosis progressing to HCC. Finally, if a watch-and-wait strategy was followed, about 22,000 of 28,765 patients with cirrhosis developed HCC. »

TABLE 2. Number of HCV Patients with SVR and Disease Progression to HCC, Per Year

	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	YEAR 6	YEAR 7	YEAR 8	YEAR 9	YEAR 10
Peginterferon-ribavirin	0	12.1	28.6	28.2	27.8	27.5	27.1	26.8	26.4	26.1
Elbasvir-grazoprevir	0	79.8	198.8	196.2	193.7	191.2	188.7	186.2	183.8	181.4
Sofosbuvir-velpatasvir	0	82.9	201.0	198.4	195.8	193.3	190.7	188.3	185.8	183.5
Sofosbuvir-ledipasvir	0	82.4	204.6	202.0	199.4	196.8	194.2	191.7	189.2	186.7

HCC indicates hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virologic response.

TABLE 3. Number of HCV Patients with SVR and Disease Progression to HCC, Per Year

	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	YEAR 6	YEAR 7	YEAR 8	YEAR 9	YEAR 10	TOTAL
Peginterferon-ribavirin	0	1344.6	2093.2	2043.6	1944.4	1842.2	1745.8	1654.4	1567.9	1485.9	15,722.0
Elbasvir grazoprevir	0	1158.3	1705.1	1637.7	1570.2	1494.8	1423.7	1356.3	1292.4	1231.7	12,950.0
Sofosbuvir-velpatasvir	0	1232.5	1696.3	1629.4	1562.3	1487.4	1416.9	1349.9	1286.4	1226.1	12,887.2
Sofosbuvir-ledipasvir	0	1233.4	1690.5	1622.9	1556.2	1481.8	1411.7	1345.2	1282.1	1222.2	12,845.9

HCC indicates hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virologic response.

Following HCV treatment with elbasvir-grazoprevir, HCC-related costs per person in year 2 were $2633, which increased to $3521 in year 3. As mentioned, this is due to the buildup of DCC from the year before. After year 3, however, HCC costs saw a steady decline and dropped down to $2068 by year 10, as **Table 4** shows. Similarly, in year 10, costs associated with HCC were only $2058 per person after treatment with sofosbuvir-velpatasvir.

We calculated the 10-year aggregated medical costs for HCC because the medical costs for HCC vary by the number of individuals who progress to HCC each year. For all DAA medications, the 10-year medical costs due to HCC treatment are similar in value and lower than in a watch-and-wait strategy or in peginterferon-ribavirin regimens. The sofosbuvir-ledipasvir regimen resulted in $24,456 in HCC-related medical costs per patient compared with around $29,900 per patient for the prevailing peginterferon-ribavirin regimen.

Treating cirrhotic patients lowers the numbers who develop HCC and thereby the associated costs. Treatment at an earlier stage of the disease reduces the chance of sequela. For example, sofosbuvir-ledipasvir would provide the largest amount of payer savings for averted HCC cases ($17,473) compared with costs for no treatment (following watch-and-wait strategies) over 10 years. These results are presented in **Table 5**.

Discussion

Although the probability of liver cancer declines with treatment success, the number of patients with SVR increases, inadvertently increasing the number of patients with HCC, and resulting in higher costs. For patients with cirrhosis, the risks and medical costs for HCC are already higher, as per clinical manifestations of disease progression and regardless of whether the patient is "cured" of HCV.[25] A patient with cirrhosis continues to accrue costs related to cirrhosis care and monitoring even with the increased efficacy of DAAs.[25]

OUR RESULTS EMPHASIZE AN URGENCY FOR PROVIDING DIRECT-ACTING ANTIVIRALS AS FIRST-LINE TREATMENT, ESPECIALLY IN PATIENTS WITH CIRRHOSIS.

The majority of costs for DAAs come from earlier stages, resulting in lower HCC-related costs with reduced disease stage progression, while for peginterferon-ribavirin, most of the medical costs are driven by liver disease complications (DCC and liver cancer). Treatment with DAAs increases the number of beneficiaries reaching SVR and reduces the risk of HCC. Plus, higher SVR means lower numbers of liver-related outcomes. Thus, as is evident in the model results, most of the HCC cases from HCV infection are observed in patients who did not reach SVR.

The number of cases of HCC in patients who were "cured" following DAA treatment are extremely high (after 10 years, there are less than 200 HCC cases with SVR out of 26,000 plus patients in the model cohort), while HCC cases without SVR are lower. HCC cases with SVR are extremely low among patients treated with peginterferon-ribavirin, and the majority of HCC cases are observed among patients who were not "cured," due to lowered efficacy of this prevailing treatment. The number of patients with HCC and "cured" are also less likely to continue through disease progression to liver transplantation and so on.

The averted high medical costs of HCC treatment are often thought to be overshadowed by the high costs of the DAAs. Therefore, high SVR rates would result in an increase in HCC-related savings and less negative liver-related health events would occur in these regimens. Thus, when the probability of SVR increased, as with DAA treatments, the likelihood of negative health outcomes fell and the number of individuals in earlier stages of cirrhosis increased.

This study focused on patients infected with HCV genotype 1a, which is the most common strain of HCV in the United States. The strength of this research is that this model incorporated some of the complexity and uncertainty involved in healthcare decision making pertinent to the ongoing debate over Medicaid coverage for HCV treatment. The key is that DAAs result in lower HCC medical spending costs than peginterferon-ribavirin and watch-and-wait regimens; peginterferon-ribavirin has lower HCC costs than watch-and-wait alone.

The lower medical costs and risks for patients with cirrhosis, and improved health outcomes from treating patients without cirrhosis, can offset the cost implications of treatment. The model demonstrates that there is almost a $156 million difference in HCC medical costs between DAAs and peginterferon-ribavirin for Medicaid patients over a 10-year period. The results also emphasize an urgency for providing DAAs as first-line treatment, especially in patients with cirrhosis. The true effectiveness of DAAs becomes evident through the reduction of HCC risk and related medical costs; patients with cirrhosis are already at higher risk for HCC and the high SVR rate associated with DAAs is imperative in improving liver health outcomes. Starting DAA treatment for patients with cirrhosis may additionally reduce the likelihood of future outcomes after development of HCC »

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TABLE 4. Medical Costs for HCC, Per Person Per Year

	YEAR 1 ($)	YEAR 2 ($)	YEAR 3 ($)	YEAR 4 ($)	YEAR 5 ($)	YEAR 6 ($)	YEAR 7 ($)	YEAR 8 ($)	YEAR 9 ($)	YEAR 10 ($)	TOTAL
Peginterferon-ribavirin	0	2860.3	4323.0	4097.8	3785.3	3482.0	3203.5	2947.4	2711.8	2495.3	29,906.3
Elbasvir grazoprevir	0	2633.7	3521.3	3283.9	3056.7	2825.3	2612.6	2416.3	2235.3	2068.4	24,653.6
Sofosbuvir-velpatasvir	0	2621.9	3503.2	3267.2	3041.4	2811.3	2599.9	2404.9	2225.0	2059.1	24,533.9
Sofosbuvir-ledipasvir	0	2623.8	3491.3	3253.8	3029.6	2800.8	1411.7	2396.5	2217.5	2052.42	24,456.2

HCC indicates hepatocellular carcinoma.

TABLE 4. Savings Due to Averted HCC Costs (reference: watch-and-wait strategy), Aggregated for 10 Years, by Treatment Regimen

TREATMENT REGIMEN	10-YEAR COSTS ($)
Watch-and-wait	Reference
Peginterferon-ribavirin	12,022.7
Elbasvir grazoprevir	17,275.4
Sofosbuvir-velpatasvir	17,472.8
Sofosbuvir-ledipasvir	17,395.1

HCC indicates hepatocellular carcinoma.

(liver transplantation, ascites, further complications of cirrhosis, etc) and/or current effects of the virus, and thus the associated costs, as patients begin to reach SVR. Treatment with DAAs holds importance for patients with cirrhosis to prevent HCC associated with HCV. ◆

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Juno Therapeutics Shelves ROCKET Trial While Kite Pharma Reports Positive Data From ZUMA-1

Surabhi Dangi-Garimella, PhD

DURING AN EARNINGS CALL ON MARCH 1, 2017, Hans Bishop, president and CEO of Seattle-based Juno Therapeutics, announced that the company decided to halt the ROCKET trial, also known as the JCAR015 trial, which was evaluating modified chimeric antigen receptor (CAR) T cells. Toxicity associated with the treatment, which resulted in 5 patient deaths, was the primary reason for the decision.

In early July 2016, the FDA asked Juno to halt the phase 2 trials of JCAR015 in patients with acute lymphocytic leukemia (ALL), citing 3 deaths from cerebral edema.[1] At that point, the company thought that fludarabine in the preconditioning regimen might be the culprit, and in a response to the FDA, Juno proposed leaving the drug out. Convinced by this response, the FDA allowed the trial to resume using cyclophosphamide alone during the preconditioning step. However, later in the year, 2 more patients in the trial developed cerebral edema, 1 of whom died. The company voluntarily halted JCAR015 again—and has not recovered. Subsequent investigations by the company identified several factors that may be responsible for the tragic deaths:

- Patient-specific factors
- Conditioning chemotherapy (fludarabine)
- The CAR-T cells

Although the company believes that experimentation with process improvements and protocol changes could allow the JCAR015 trial to proceed, it would need to reestablish safety and dose through another phase I study, which would further delay progress.

"2016 was a year of progress and learning for Juno and the cancer immunotherapy field," Bishop said on the earnings call. "We continue to experience encouraging signs of clinical benefit in our trial addressing NHL [non-Hodgkin's lymphoma], but we also recognize the unfortunate and unexpected toxicity we saw in our trial addressing ALL with JCAR015." The company plans to evaluate a "defined cell product" candidate in adult ALL in 2018.

Meanwhile, Kite Pharma announced that median overall survival (OS) was not reached at a median follow-up of 8.7 months in the company's ZUMA-1 trial.[2] The trial, being conducted in patients with chemotherapy-resistant aggressive B-cell NHL, is testing axicabtagene ciloleucel (previously referred to as KTE-C19). Interim analysis of the data showed that the trial met its primary endpoints of objective response rate (ORR), complete response (CR), and partial response (PR) following a single infusion of axicabtagene ciloleucel.

Of the 101 trial participants, 41% achieved ORR at 6 months (P <.0001), 36% had a CR, and 5% had a durable PR. One of the partial responders became a complete responder at 9 months following infusion. More importantly, the trial had not yet reached a median OS at this point.

The following grade 3 or higher adverse events were reported from the trial:

- Anemia (43%)
- Neutropenia (39%)
- Decreased neutrophil count (32%)
- Febrile neutropenia (31%)
- Decreased white blood cell count (29%)
- Thrombocytopenia (24%)
- Encephalopathy (21%)
- Decreased lymphocyte count (20%)
- Grade 3 or higher cytokine release syndrome, very commonly observed with CAR-T treatment, decreased from 18% to 13%.

No cases of cerebral edema were reported, unlike the JCAR015 trial.

"Several patients we treated at Moffitt Cancer Center experienced a rapid and durable complete response with this first-of-its kind therapy," Frederick L. Locke, MD, ZUMA-1 co-lead investigator, and director of research for the Immune Cell Therapy Program at Moffitt Cancer Center, said in a statement. "The ZUMA-1 study results suggest that axicabtagene ciloleucel could become a new standard-of-care for patients with refractory aggressive lymphoma."

The company is planning to submit a rolling Biologics License Application based on these results by the end of the first quarter of 2017. ◆

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Exercise Most Powerful Lifestyle Factor in Improving Breast Cancer Outcomes

Christina Mattina

A RECENT LITERATURE REVIEW EXAMINED the body of research on lifestyle changes that can reduce the risk of recurrence or death among women diagnosed with breast cancer. Exercise was found to be the strongest protective factor for both outcomes.

Researchers identified and assessed 67 articles that studied the association between breast cancer recurrence or mortality and a variety of factors, including diet, exercise, weight loss, smoking, alcohol, and vitamin intake. Their findings have been summarized in the *Canadian Medical Association Journal*.[1]

The most significant factor was physical exercise, which reduced the risks of recurrence and mortality. These effects were even stronger for women who were postmenopausal, had a body mass index above 25, and who met the recommended levels of activity as specified by cancer society guidelines. The researchers noted that adherence to these recommendations is generally low, as patients' physical activity tends to decrease after a breast cancer diagnosis, making the development of initiatives to encourage exercise in this population especially crucial.

WEIGHT GAIN BEFORE AND AFTER DIAGNOSIS WAS STRONGLY LINKED TO POORER BREAST CANCER OUTCOMES, IN TERMS OF RECURRENCE AND MORTALITY.

Weight gain before and after diagnosis was strongly linked to poorer breast cancer outcomes, again in terms of recurrence and mortality. There were no conclusive findings on whether weight loss could improve these outcomes, but the authors noted that longer-term studies that are currently underway could provide additional insight into these effects.

Smoking was another factor that increased the risk of death from breast cancer, as women who continued to smoke after diagnosis had higher mortality rates than those who had never smoked and women who quit after being diagnosed, albeit to a lesser extent. Evidence was insufficient to determine that smoking increases the risk of breast cancer recurrence. As for alcohol consumption, the effects could not be definitively determined. As some studies have indicated a link between alcohol and cancer recurrence, the authors recommended that restricting the consumption of alcohol "is a worthwhile goal to reduce the risk of a second primary breast cancer." »

The body of evidence surrounding diet and vitamin intake did not yield many conclusive findings either. Vitamins C and D and soy products could potentially reduce breast cancer recurrence or mortality, but randomized trials are needed to confirm the preliminary findings. There was no association found between breast cancer outcomes and vitamin E intake or a "prudent diet," defined as a diet high in fruits, vegetables, whole grains, and chicken.

Overall, the researchers concluded that the current literature provides the strongest support for interventions that encourage women to exercise more and quit smoking. They noted that a cancer diagnosis could present an opportunity for a "teachable moment" in which a woman might be more motivated to change her lifestyle. Still, the benefits potentially experienced from these lifestyle changes cannot completely counteract the effects of a tumor, and outcomes will be different for every patient.

"Patients should not be made to feel that inadequate lifestyle changes have led to recurrence of their cancer," the authors warned. ◆

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Insurance Status, Race, and Education Remain Persistent Barriers to Cancer Screening

Surabhi Dangi-Garimella, PhD

THE RESULTS OF A NEW REPORT that monitored cancer screening rates between 2000 and 2015, using data from the National Health Interview Survey (NHIS), show that colorectal cancer screening rates have seen recent progress toward achieving the Healthy People 2020 (HP2020) objectives, breast cancer screening rates have remained static, and cervical cancer screening rates have been declining. According to the study, published in *Morbidity and Mortality Weekly Report*, race, education, income, and insurance status were significant determinants of disparity among participants.

The authors analyzed NHIS data—a nationally representative sample of the civilian, noninstitutionalized population residing in the United States—information on the household, each person in the family residing in that household, and a randomly selected sample of adults (≥18 years) and children (if present) from each family.

With a focus on cancer screening, adults were asked if they had undergone screening, and those who responded in the affirmative were asked to date their latest screening test. For this study, information on the following tests was gathered:

- Mammography within 2 years for women aged 50 to 74 years
- Papanicolaou (Pap) test within 3 years for women without a hysterectomy and aged 21 to 65 or Pap test with human papillomavirus test within 5 years for women without a hysterectomy and aged 30 to 65 years
- Fecal occult blood test within 1 year, sigmoidoscopy within 5 years, and fecal occult blood test within 3 years, or colonoscopy within 10 years for respondents aged 50 to 75 years

The authors evaluated screening trends over time using NHIS data from 2000, 2003, 2005, 2008, 2010, 2013, and 2015. Of the 55.2% of adults who responded, mammography use was found to be stable from 2000 to 2015. In 2015, 71.5% of women aged 50 to 74 years had a mammogram, which was below the HP2020 target of 81.1%. Racial disparity was evident, with American Indians/Alaska natives reporting the lowest rate of screening (56.7%). Women who were born outside the United States and had been living in the country for less than 10 years had lower rates (53.7%) than those who were born in the United States (72.1%). Further, not surprisingly, uninsured women and those without a usual source of healthcare reported very low rates (35.3% and 32.9%, respectively).

Cervical cancer screening rates saw an overall decline from 2000 to 2015, reaching just 83% in 2015, which was 10% below the HP2020 target. Asian women had the lowest rates of screening (75.8%). When compared by age groups, younger women, between 21- and 30-years old had low rates of screening (78.3%); the authors also found that women born outside the United States had low screening rates. Insurance trends persisted: only 65.1% of women who lacked a usual source of healthcare and 63.8% of uninsured women.

Colorectal cancer screening increased from 2000 to 2015, but did not achieve the HP2020 target of 70.5%. Screening rates were lowest among American Indians and Alaska natives (48.4%) and Hispanics (47.4%). Screening rates were also lower in the 50-to-64 age group (57.9%) compared with the 65-to-75 age group (71.8%). Education and insurance coverage were significant determinants of increased screening rates.

The authors write, "Innovative approaches are needed to reach some racial and ethnic minorities and medically underserved populations to improve the use of cancer screening tests toward the HP2020 targets." ◆

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Concerning Trends in Colorectal Cancer Incidence Among Younger Adults

Christina Mattina

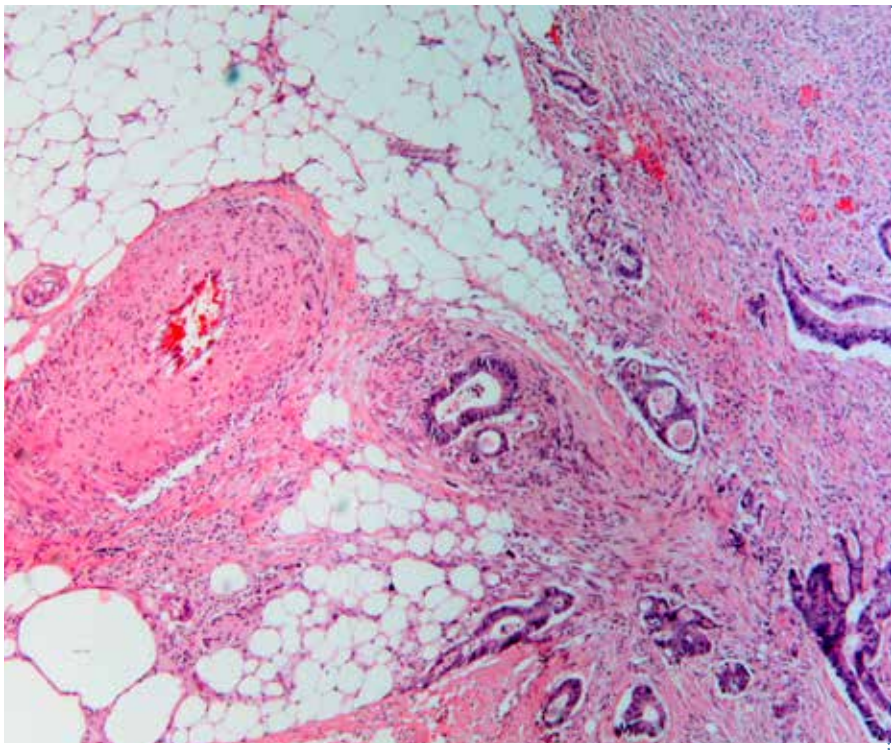
THE INCIDENCE OF COLORECTAL CANCER (CRC) continues to decline for older Americans, but researchers have noticed a significant uptick in prevalence among young adults. In one of the most striking findings, the age-specific risk of CRC for the youngest cohort is now as high as it was among those born more than a century earlier, circa 1890.

Using CRC incidence data from 1974 to 2013, researchers created birth cohort models to illustrate age-specific incidence and risk. The study, published in the *Journal of the National Cancer Institute* (*JNCI*),[1] was the first since 1994 to assess CRC trends by time period and birth cohort.

Their findings pointed to improvements in older age groups but troubling patterns among young adults. For example, beginning in the mid-1980s, rates of colon cancer declined among those aged 55 or older, but increased 1.0% per year in adults aged 30 to 39 years and 2.4% each year for adults aged 20 to 29 years. The surge in rectal cancer incidence was even sharper, as it decreased 2% per year for those aged 75 and older but increased 4% annually for people in their 20s. The age-adjusted proportion of incident cases for those aged 55 and younger doubled from 14.6% in 1989-1990 to 29.2% in 2012-2013.

WHEREAS OVERALL SCREENING AND DETECTION RATES [FOR COLORECTAL CANCER] HAVE INCREASED OVER TIME, THESE TRENDS LIKELY DO NOT ACCOUNT FOR AGE-RELATED TRENDS.

One of the most alarming findings was related to age-specific trends. The cohort born circa 1890 had double the age-specific risk of colon cancer and triple the risk of rectal cancer compared with those born in 1950. These risks declined in the first half of the 20th century, then began to rise until the age-specific risk for the youngest cohort born circa 1990 was equivalent to that of the 1890 birth cohort. »



TUMOR INVASION INTO VEIN IN A CASE OF COLORECTAL CANCER

These findings take on further urgency when considering the complexity of CRC and the scarcity of treatment options that successfully increase survival. At the annual meeting of the National Comprehensive Cancer Network, oncologist Alan P. Venook, MD, explained that while there have been improvements in CRC diagnosis, "a sum of all treatments that have been developed over the last decade finds that 10-month OS [overall survival] seems the most that has been achieved."[2]

The authors of the *JNCI* study noted that whereas overall screening and detection rates have increased over time, these trends likely do not account for age-related trends, as younger people are still less likely to be screened. Additionally, incidences of both early stage and advanced-stage cancers have risen at about the same rate, indicating that screening was not a significant factor.

Instead, the researchers wrote, lifestyle changes are a likely culprit for the spike in CRC among young adults. Younger generations have lower levels of smoking and alcohol consumption, but are more likely to have excess body fat driven by unhealthy diets and sedentary lifestyles, which are known risk factors for the disease. These adults are also more likely to be uninsured and less likely to bring up cancer as a concern with their providers. Therefore, increased education about the risks of CRC for both patients and clinicians, along with expanded access to care and screening, could help reverse these trends among young people. The researchers also suggested evaluating the possibility of revising guidelines to recommend an earlier starting point for screening practices, such as age 45 years instead of 50.

"These results highlight the need for etiologic research to elucidate causes for the underlying increase in disease risk in young birth cohorts, as well as creative new strategies to curb the obesity epidemic and shift Americans toward healthier eating and more active lifestyles," the study authors concluded. "Beyond awaiting scientific discovery and the widespread adoption of healthier living, meaningful action can be taken to mitigate premature morbidity and mortality from this disease through educational campaigns about the importance of timely follow-up of CRC symptoms, regardless of patient age, and age-appropriate screening." ◆

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Smilow's In-House Pharmacy Saved Costs, Beneficial to Patients

Surabhi Dangi-Garimella, PhD

EXPANDING A HEALTH-SYSTEM pharmacy's operations to include specialty drugs, namely oral oncology agents, improved patient care by reducing errors and saving costs. The hospital channeled the costs to improve patient education, monitoring, and assistance.

The study, which was presented at the American Society of Clinical Oncology's Quality Care Symposium, was conducted at Smilow Cancer Hospital at Yale-New Haven.[1] The cancer center, which has implemented a Quality Oncology Practice Initiative, or QOPI, certification process, identified several drawbacks with its oral oncologic process:

- Lack of documentation in the electronic health record
- Involvement of third-party pharmacies for patient refills
- Incorrect self-administration due to lack of education
- Delivery delays
- High co-pays
- Underuse of patient assistance programs

"Prior to our in-house pharmacy, we had no idea what happened after we sent prescriptions to outside specialty pharmacies," said lead author Kerin Adelson, MD, assistant professor of medicine and chief quality officer for Smilow Cancer Hospital at Yale-New Haven.[2] "Did the patient start treatment later than recommended? Did the patient take the right combination and on a consistent basis? These were all questions that affect quality and outcomes that we were not able to answer before."

In an attempt to correct these issues, the hospital developed a task force, which created a program that would expedite drug access, standardize consent, and ensure clinical support for patients. A new policy routes the treatment protocol for oral oncologic agents to a clinical oncology pharmacy and the specialty pharmacy. The orders are verified by the nursing team and the pharmacy team and pharmacists call on patients at pre-specified intervals to monitor adherence and treatment-related toxicity. The hospital's Medication Assistance Program provided co-pay support.

Implementation of the modified protocol resulted in 80% of patients receiving their medication within 72 hours, as opposed to waiting for 2 to 3 weeks, and has so far prevented 400 prescription errors. Monitoring is much more stringent and specialty pharmacists at Smilow monitor patients even if they fill their prescriptions at another pharmacy.

The hospital has also witnessed significant cost savings. Since its inception in February 2015, the oral chemotherapy program at Smilow has earned $44 million in revenue, with a margin of $9 million. The hospital also provides co-pay assistance to an average of 140 patients each month.

Highlighting the importance of vigilance, whether patients receive oral agents or intravenous infusions, Howard Cohen, BSPharm, MS, FASHP, associate director of oncology pharmacy services at Yale-New Haven, "With our protocol, we are able to better address medication adherence and side effects—all of which translates to a higher quality of care for our patients." ◆

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Value-based Payment Models in Oncology: Will They Help or Hinder Patient Access to New Treatments?

Sonal Shah, PharmD, and Greg Reh

continued from cover

Deloitte.

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Sonal Shah, PharmD, is senior manager, Deloitte Center for Health Solutions.

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In addition, CMS recently launched the Oncology Care Model (OCM), a 2-part payment system, resembling a PCMH and a bundled payment model. Many of these models target drug spending.

The Deloitte Center for Health Solutions recently interviewed 18 individuals from health plans, provider groups, and clinical pathway developers that are participating, supporting, or evaluating oncology payment models to understand what approaches are perceived to be working, and what the early results (financial and clinical) have been. We also sought to understand how these payment models affect the use of new treatments. With rapid advances in diagnostics, precision medicine, and immunotherapy, how can a standardized payment model be defined that leaves room for innovation? Our research revealed that many organizations are experimenting with value-based payment models that aim to balance the competing goals of controlling costs and allowing access to advances in treatment. While none of the participating organizations claimed to have solved this equation, all of them indicated that they had seen early signs of success and were working to evolve and expand these models.

How Do Value-based Payment Models Influence Drug Use and Spending?

Value-based payment models can influence prescribing primarily through 2 mechanisms:

1. Using evidence-based clinical pathways to provide decision-making support
2. Including drug costs as part of bundled payment models, including the OCM.

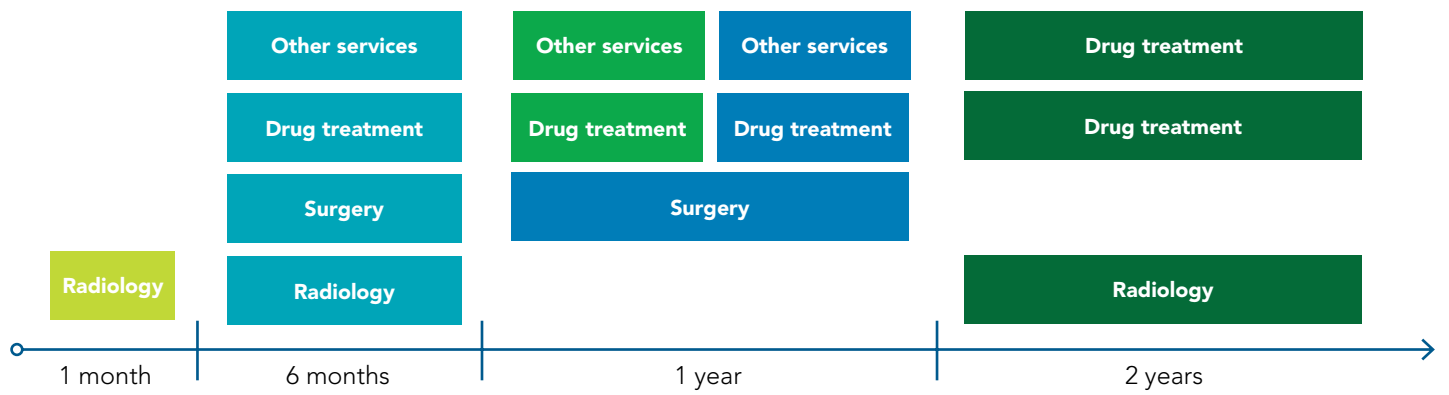
Clinical pathways. All the providers we interviewed were implementing clinical pathways to steer prescribers to the most cost-effective drug treatments, regardless of payment model participation. These providers were evaluating compliance with evidence-based pathways to find opportunities for savings on drug spending. Implementing a clinical pathway tool is typically among the first steps for providers participating in any of the payment models we evaluated.

Both health plans and physician practices can develop and administer clinical pathways. Either way, prescribers are held to a goal of adhering to pathways 70% to 85% of the time, allowing for some flexibility for variability in care that might result from patient characteristics, preferences, or the introduction of new treatments.

Among the physicians we interviewed, on- or off-pathway status influenced their prescribing patterns, especially when pathway status was directly tied to reimbursement. Off-pathway drugs might require additional prior authorization, which creates administrative burdens for providers who choose those drugs. Some physicians we interviewed expressed resistance to adopting pathways, because they did not want to be in a situation where they could not treat a patient with a novel therapy that is not yet on an approved clinical pathway. More frequent updates to clinical pathways could reduce delays in adopting new therapies.

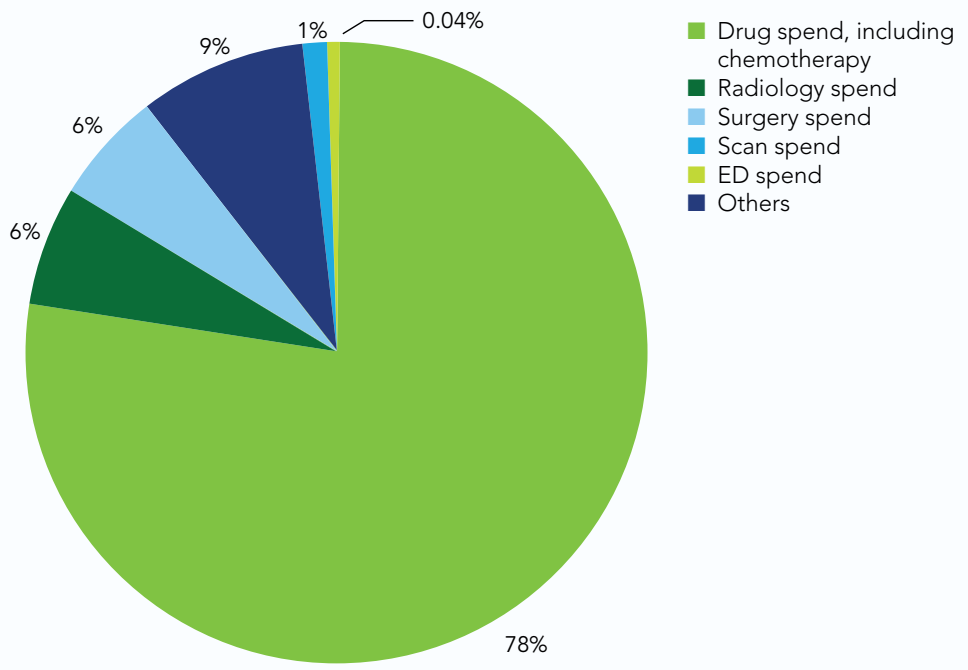
Bundled payments. The cost of drugs is calculated directly into reimbursement for the majority of bundled payment models being piloted. Participants in these programs told us that their bundles varied from covering the cost of 1 service, to covering all services over a 1-month or up to a 2-year time frame (**Figure 1**). Almost everyone interviewed participating in a bundled payment model included drug treatment as part of the bundle, though most providers were not taking on downside risk.

FIGURE 1. Examples of Different Bundle Types Implemented by Participating Organizations



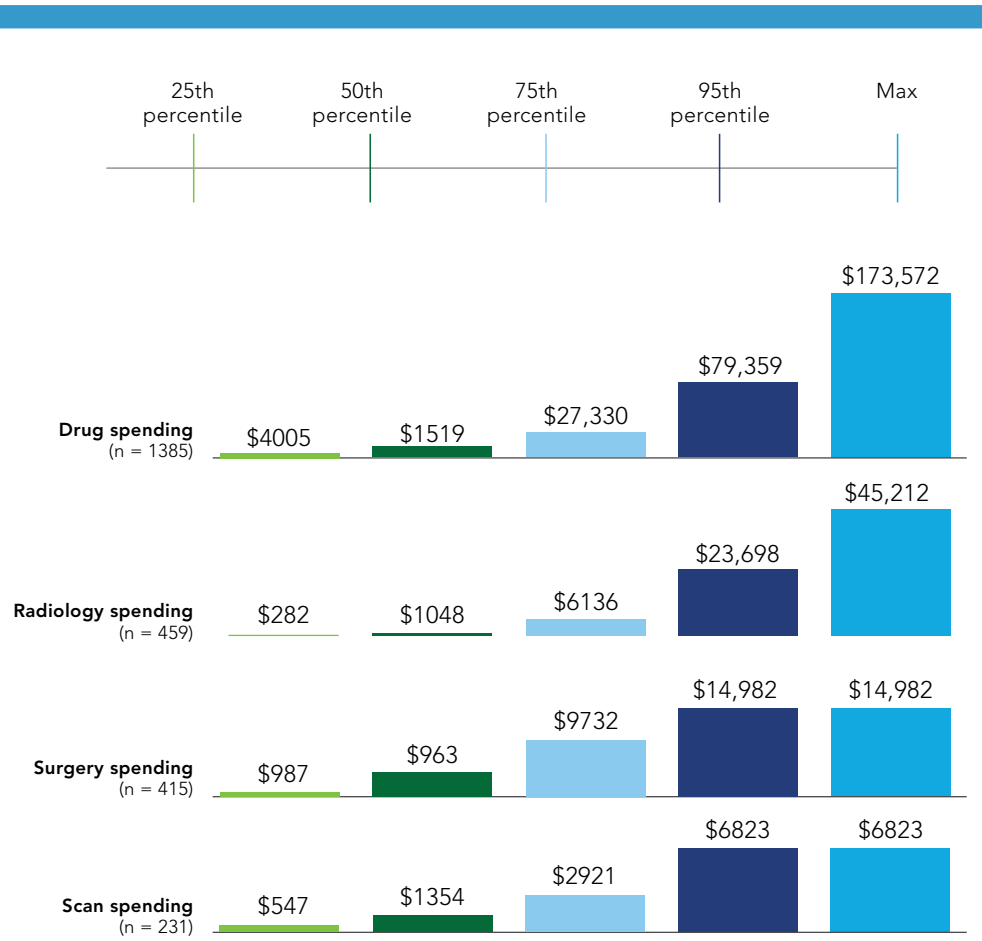
FFS indicates fee-for-service; OCM, Oncology Care Model. Source: Deloitte Center for Health Solutions analysis.

FIGURE 2. Breakdown of Spending in a Breast Cancer Episode During a 6-Month Period From the Initiation of Chemotherapy



ED indicates emergency department.
Source: Deloitte analysis of 2013-2014 Truven MarketScan commercial claims data for stage I breast cancer patients, episodes starting from first dose of chemotherapy plus 6 months.

FIGURE 3. Distribution of Spending Across Key Service Categories With the Breast Cancer Episode[a]



[a]Variation is shown for only the episodes that included spending on each service. The number of episodes that include radiology, surgery, and scan spending are indicated in parentheses.

Source: Deloitte analysis of 2013-2014 Truven MarketScan commercial claims data for stage 1 breast cancer patients, episodes starting from first dose of chemotherapy plus 6 months.

Several health plans said they were experimenting with different approaches to allow flexibility for providers using expensive new treatments. These approaches include precisely defining bundles based on cancer stage and biomarker status, adjusting bundle prices frequently, carving-out new treatments, and incorporating a stop-loss provision to reduce financial risk to the provider after spending hits a certain threshold.

Other health plan leaders and providers we interviewed were strongly opposed to bundled payments for oncology. These interviewees expressed concern about the underlying complexities of standardizing a bundle for a disease where variation is normal, due to patient and disease characteristics, particularly when patient volumes for any particular bundle are low. Furthermore, they were worried about the unpredictability of drug costs, especially given the recent pace of innovative new drugs entering the market. One health system leader was concerned that a bundled payment model could force physicians in his organization to decide about using a new treatment based on financial constraints.

OCM. The risk-sharing component of CMS's OCM is initiated at the start of chemotherapy, and includes the costs for chemotherapy and other services for 6 months. Organizations participating in the OCM started with a 1-sided risk arrangement, and were allowed to take on 2-sided risk starting January 1, 2017. Under the Medicare Access and [Children's Health Insurance Program] CHIP authorization Act (MACRA), clinicians participating in advanced alternative payment models (APMs), including OCM with 2-sided risk, will receive a 5% increase in their Medicare payments. This increase would be in addition to potential shared savings or performance bonuses that APMs may produce. Those we interviewed expressed an interest in eventually moving towards 2-sided risk arrangements so they can take advantage of these financial incentives. MACRA could spur additional interest from providers in participating in this payment model.

The increased interest in OCM is important to highlight since the majority of savings across the measured 6-month period is expected to come from drug spending. We analyzed 2013-2014 Truven MarketScan[2] commercial claims data for stage I breast cancer patients to identify spending (defined as the total claims paid by commercial insurers) variance across major service areas. Claims were categorized into episodes, including all services over a 6-month period and initiated by chemotherapy, mimicking the definition of an OCM episode. The primary focus was on patients with stage I disease, since this early stage is least likely to be associated with significant clinical variation and associated variability in spending.

For the 1385 identified episodes of cancer, the average spending per episode was $30,000—the range was $500 to $200,000. A majority of spending was on drugs, including all drugs prescribed and administered in the inpatient or outpatient setting, with retail and over-the-counter drugs were excluded (**Figure 2**). Further, most of the variability in cost across the total episode comes from drug spending, followed by surgery, and radiology (**Figure 3**).

What Have Been the Financial Savings From These Payment Models?

Many new payment models have shown some early, but varied, success in reducing the cost of cancer care (**Table**). Most of those interviewed attribute this success to a combination of elements: more efficient use of evidence-based pathways, increased access to lower-cost care settings, reduced need for managing patients in the emergency department or in-patient facilities, and proactive care planning. Notably, all those interviewed suggested that the use of clinical pathways was a driver of financial savings, either directly through reduced drug spending or indirectly through more appropriate patient treatment.

Will New Value-based Payment Models Pose Challenges for Adoption of New Treatments?

Currently, the impact of value-based payment models on new treatments is unclear. The implementation of evidence-based »

TABLE. Drivers of Financial Savings and Results to Date[3]

MODEL	STATED DRIVERS OF SAVINGS (RANGES ACROSS PILOTS)[a]	EXAMPLES (SAVINGS REALIZED)
Financial incentives for adhering to clinical pathways	• Reduced drug spending (5%-37%) • Reduced toxicity, resulting in: o Lower ED visits (6%-40%) o Reduced admissions (7%-36%)	• Model 1: Reduction in drug costs of 37% over the course of a 12-month study • Model 2: 10% lower 1-year cost per patient • Model 3: Estimated 3%-4% reduction in total cost of care per year
PCMH	• Greater physician accountability and increased consistency in care • Reduced ED utilization (48%-68%) • Reduced admissions (34%-51%) • Reduced LOS (21%-44%) • Improvements in EOL care; increase in length of time in hospice care (34%)	• Model 1: 35% annual reduction in total cost of care • Model 2: Estimated savings to the health plan of $1 million per physician per year • Model 3: $550 savings per patient in the first year
Bundles	• Reduced ED visits (30%) • Reduced admissions[b] • Reduced in-patient days (17%) • Flattening out drug spending after historic increase of 15%-18% per year	• Model 1: Initial pilot savings of 34% in total costs. Spending for chemotherapy up almost 179% • Model 2: Reduction in PMPM costs; lower increases in oncology drug costs
Specialty ACOs	• Reduced drug spending due to pathways adherence (5%) • Reduced readmissions[b] • Reduced length of stay[b] • Reduced radiation therapy[b]	• Model 1: Overall savings of ~2% in the first year, with greater savings anticipated following expansion of the program to focus on additional services over subsequent years

ACO indicates accountable care organizations; ED, emergency department; EOL, end-of-life care; LOS, length of stay; PCMH, patient-centered medical home; PMPM, per member per month.
[a]Ranges reflect the high and low end of reported results across pilots within a payment model type.
[b]Quantified data unavailable.

pathways as part of value-based payment models could, in some instances, increase the use of new treatments. On the other hand, payment models that emphasize financial goals could deter physicians from prescribing expensive therapies.

Quality measures included in new payment models may also drive prescribing behavior. Short-term measures or those with a narrow focus could make it difficult to recognize and reward the value that new treatments may offer. Without a way to capture this benefit, physicians may choose to avoid costly treatments in an attempt to meet financial metrics. As payment models evolve, quality measures should reflect the value of innovation and focus on things that matter most to patients.

Diagnostics will likely become increasingly valuable in cancer care as our understanding of tumor adaptation and drug targets continues to expand. The applications of diagnostics are rapidly expanding beyond simply determining appropriate use of individual targeted therapies. Genomic testing, immuno-sequencing, and other diagnostics can determine the profile of a patient's cancer and identify a set of treatment options that patients are most likely to respond to. New treatments, including immunotherapies, which harness the patient's immune system to identify and attack cancer cells, may become more tailored and targeted to address mutations in cancers resistant to other treatments. In the near-term, these advances in diagnostics and treatment may continue to increase spending in oncology. However, in the future, dynamic clinical-decision support tools that consider multiple patient variables and also consider the financial trade-offs of treatment choices can help direct prescribers to treatments that can optimize patient outcomes and reduce cost over the long term.

Conclusions

Early experiments with value-based payment models show some promise, and as providers invest in data, analytics, and patient-centered care, their willingness to participate in value-based payment models is likely to expand. Investments in data analytics may help providers identify opportunities to reduce variability in cost and outcomes, increasing their comfort in accepting downside risk. However, as payment models evolve they should incorporate quality measures that capture the value that new treatments can bring so that financial incentives alone do not drive prescribing.

Many stakeholders across the ecosystem are investing in new technologies such as artificial intelligence and blockchain to help illuminate which drugs work in specific patient populations, and under what circumstances. Access to such information could guide the use of new drugs and treatments, improve health outcomes, and reduce spending. ◆

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Greg Reh leads the global and US life sciences practices for Deloitte. Greg has more than 25 years of experience helping clients in the life sciences, process manufacturing, consumer, and government sectors. In his role consulting to clients, his career has spanned such topics as technology strategy, integration solution development, and implementation of emerging and disruptive technology.

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1. Cancer costs projected to reach at least $158 billion in 2020 [press release]. Bethesda, MD: National Cancer Institute; January 12, 2011. https://www.nih.gov/news-events/news-releases/cancer-costs-projected-reach-least-158-billion-2020. Accessed February 9, 2017.
2. Data on file. Copyright Ó 2014 Truven Health Analytics Inc., an IBM Company. All Rights Reserved.
3. Deloitte analysis of secondary literature and interview findings.

The **new permanent J-code for DARZALEX® (daratumumab)** is effective as of January 1, 2017.[1]

J9145	Injection, daratumumab, 10 mg

- J9145 will replace miscellaneous and/or temporary codes that were previously used across various sites of care*
- J9145 applies to commercial and Medicare patients in both hospital outpatient and physician's office settings[1]

Please note, the fact that a drug, device, procedure, or service is assigned an HCPCS† code and a payment rate does not imply coverage by the Medicare program. An HCPCS code and a payment rate indicate only how the product, procedure, or service may be paid if covered by the program. Fiscal Intermediaries/Medicare Administrative Contractors determine whether a drug, device, procedure, or other service meets all program requirements for coverage.[2]

The information provided represents no statement, promise, or guarantee of Janssen Biotech, Inc., concerning levels of reimbursement, payment, or charge. Please consult your payer organization with regard to local or actual coverage, reimbursement policies, and determination processes. Information is subject to change without notice. Nothing herein may be construed as an endorsement, approval, recommendation, representation, or warranty of any kind by any plan or insurer referenced herein. This communication is solely the responsibility of Janssen Biotech, Inc. Information is valid as of January 1, 2017, and is subject to change.

For more information please visit www.darzalexhcp.com

Indication

DARZALEX® is a CD38-directed cytolytic antibody indicated:

- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy
- as monotherapy, for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

Important Safety Information

Warnings and precautions include: infusion reactions, interference with serological testing, neutropenia, thrombocytopenia, and interference with determination of complete response

- In patients who received Darzalex® in combination with lenalidomide and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: neutropenia (92%), thrombocytopenia (73%), upper respiratory tract infection (65%), infusion reactions (48%), diarrhea (43%), fatigue (35%), cough (30%), muscle spasms (26%), nausea (24%), dyspnea (21%) and pyrexia (20%). The overall incidence of serious adverse reactions was 49%. Serious adverse reactions were: pneumonia (12%), upper respiratory tract infection (7%), influenza (3%) and pyrexia (3%).
- In patients who received Darzalex® in combination with bortezomib and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: thrombocytopenia (90%), neutropenia (58%), peripheral sensory neuropathy (47%), infusion reactions (45%), upper respiratory tract infection (44%), diarrhea (32%), cough (27%), peripheral edema (22%), and dyspnea (21%). The overall incidence of serious adverse reactions was 42%. Serious adverse reactions were: upper respiratory tract infection (5%), diarrhea (2%) and atrial fibrillation (2%).

Please see Full Important Safety Information on next page and Brief Summary of Full Prescribing Information on adjacent page.

References: 1. Department of Health and Human Services: Centers for Medicare & Medicaid Services. Federal Register: Rules and Regulations. November 2, 2016; 81(219): 79562-7989.
2. Medicare National Coverage Determinations Manual. Centers for Medicare & Medicaid Services (CMS); May 16, 2016.

*Please check with individual payers and carriers for specific documentation and guidance when billing for a new drug.

†Healthcare Common Procedure Coding System.

DARZALEX®
(daratumumab)
injection for intravenous infusion
100 mg/5 mL, 400 mg/20 mL

Important Safety Information

CONTRAINDICATIONS - None

WARNINGS AND PRECAUTIONS

Infusion Reactions

- DARZALEX® can cause severe infusion reactions. Approximately half of all patients experienced a reaction, most during the first infusion. Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing an infusion. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension.
- Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt infusion for reactions of any severity and institute medical management as needed. Permanently discontinue therapy for life-threatening (Grade 4) reactions. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.
- To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients following DARZALEX® infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Interference with Serological Testing

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

Neutropenia

- DARZALEX® may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX® dose delay may be required to allow recovery of neutrophils. No dose reduction of DARZALEX® is recommended. Consider supportive care with growth factors.

Thrombocytopenia

- DARZALEX® may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. DARZALEX® dose delay may be required to allow recovery of platelets. No dose reduction of DARZALEX® is recommended. Consider supportive care with transfusions.

Interference with Determination of Complete Response

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

Adverse Reactions

- In patients who received DARZALEX® in combination with lenalidomide and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: neutropenia (92%), thrombocytopenia (73%), upper respiratory tract infection (65%), infusion reactions (48%), diarrhea (43%), fatigue (35%), cough (30%), muscle spasms (26%), nausea (24%), dyspnea (21%) and pyrexia (20%). The overall incidence of serious adverse reactions was 49%. Serious adverse reactions were pneumonia (12%), upper respiratory tract infection (7%), influenza (3%) and pyrexia (3%).
- In patients who received DARZALEX® in combination with bortezomib and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: thrombocytopenia (90%), neutropenia (58%), peripheral sensory neuropathy (47%), infusion reactions (45%), upper respiratory tract infection (44%), diarrhea (32%), cough (27%), peripheral edema (22%), and dyspnea (21%). The overall incidence of serious adverse reactions was 42%. Serious adverse reactions were upper respiratory tract infection (5%), diarrhea (2%) and atrial fibrillation (2%).

DRUG INTERACTIONS

Effect of Other Drugs on Daratumumab

- The coadministration of lenalidomide or bortezomib with DARZALEX® did not affect the pharmacokinetics of daratumumab.

Effect of Daratumumab on Other Drugs

- The coadministration of DARZALEX® with bortezomib did not affect the pharmacokinetics of bortezomib.

Please see Brief Summary of Full Prescribing Information on adjacent page.

janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

DARZALEX®
(daratumumab)
injection for intravenous infusion
100 mg/5 mL, 400 mg/20 mL

DARZALEX® (daratumumab) injection, for intravenous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

DARZALEX is indicated:

- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.
- as monotherapy, for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion Reactions

DARZALEX can cause severe infusion reactions. Approximately half of all patients experienced a reaction, most during the first infusion.

Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion.

Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension *[see Adverse Reactions].*

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy for life-threatening (Grade 4) reactions. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion *[see Dosage and Administration (2.1) in Full Prescribing Information].*

To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients following DARZALEX infusions *[see Dosage and Administration (2.2) in Full Prescribing Information].* Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum[1] *[see References].* The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions].*

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX.

Neutropenia

DARZALEX may increase neutropenia induced by background therapy *[see Adverse Reactions].*

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX dose delay may be required to allow recovery of neutrophils. No dose reduction of DARZALEX is recommended. Consider supportive care with growth factors.

Thrombocytopenia

DARZALEX may increase thrombocytopenia induced by background therapy *[see Adverse Reactions].*

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. DARZALEX dose delay may be required to allow recovery of platelets. No dose reduction of DARZALEX is recommended. Consider supportive care with transfusions.

Interference with Determination of Complete Response

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

ADVERSE REACTIONS

The following serious adverse reactions are also described elsewhere in the labeling:

- Infusion reactions *[see Warning and Precautions].*
- Neutropenia *[see Warning and Precautions].*
- Thrombocytopenia *[see Warning and Precautions].*

Adverse Reactions in Clinical Trials

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

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 717 patients with multiple myeloma including 526 patients from two Phase 3 active-controlled trials who received DARZALEX in combination with either lenalidomide (DRd, n=283; Study 3) or bortezomib (DVd, n=243; Study 4) and four open-label, clinical trials in which patients received DARZALEX either in combination with lenalidomide (n=35), or as monotherapy (n=156).

Combination Treatment with Lenalidomide

Adverse reactions described in Table 1 reflect exposure to DARZALEX (DRd arm) for a median treatment duration of 13.1 months (range: 0 to 20.7 months) and median treatment duration of 12.3 months (range: 0.2 to 20.1 months) for the lenalidomide group (Rd) in Study 3. The most frequent adverse reactions (≥20%) were infusion reactions, diarrhea, nausea, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, cough and dyspnea. The overall incidence of serious adverse reactions was 49% for the DRd group compared with 42% for the Rd group. Serious adverse reactions with at least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (12% vs Rd 10%), upper respiratory tract infection (7% vs Rd 4%), influenza and pyrexia (DRd 3% vs Rd 1% for each).

Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% (n=22) in the Rd arm.

Table 1: Adverse reactions reported in ≥ 10% of patients and with at least a 5% frequency greater in the DRd arm in Study 3

Adverse Reaction	DRd (N=283) %			Rd (N=281) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Infusion reactions[a]	48	5	0	0	0	0
Gastrointestinal disorders						
Diarrhea	43	5	0	25	3	0
Nausea	24	1	0	14	0	0
Vomiting	17	1	0	5	1	0
General disorders and administration site conditions						
Fatigue	35	6	< 1	28	2	0
Pyrexia	20	2	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[b]	65	6	< 1	51	4	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	26	1	0	19	2	0
Nervous system disorders						
Headache	13	0	0	7	0	0
Respiratory, thoracic and mediastinal disorders						
Cough[c]	30	0	0	15	0	0
Dyspnea[d]	21	3	< 1	12	1	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.

[b] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment from baseline listed in Table 2.

Table 2: Treatment-emergent hematology laboratory abnormalities in Study 3

	DRd (N=283) %			Rd (N=281) %		
	Any Grade	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Anemia	52	13	0	57	19	0
Thrombocytopenia	73	7	6	67	10	5
Neutropenia	92	36	17	87	32	8
Lymphopenia	95	42	10	87	32	6

Key: D=Daratumumab, Rd=lenalidomide-dexamethasone.

Combination Treatment with Bortezomib

Adverse reactions described in Table 3 reflect exposure to DARZALEX (DVd arm) for a median treatment duration of 6.5 months (range: 0 to 14.8 months) and median treatment duration of 5.2 months (range: 0.2 to 8.0 months) for the bortezomib group (Vd) in Study 4. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, peripheral edema, upper respiratory tract infection, peripheral sensory neuropathy, cough and dyspnea. The overall incidence of serious adverse reactions was 42% for the DVd group compared with 34% for the Vd group. Serious adverse reactions with at least a 2% greater incidence in the DVd arm compared to the Vd arm were upper respiratory tract infection (DVd 5% vs Vd 2%), diarrhea and atrial fibrillation (DVd 2% vs Vd 0% for each).

Adverse reactions resulted in discontinuations for 7% (n=18) of patients in the DVd arm versus 9% (n=22) in the Vd arm.

Table 3: Adverse reactions reported in ≥ 10% of patients and with at least a 5% frequency greater in the DVd arm Study 4

Adverse Reaction	DVd (N=243) %			Vd (N=237) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Infusion reactions[a]	45	9	0	0	0	0
Gastrointestinal disorders						
Diarrhea	32	3	< 1	22	1	0
Vomiting	11	0	0	4	0	0
General disorders and administration site conditions						
Edema peripheral[b]	22	1	0	13	0	0
Pyrexia	16	1	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[c]	44	6	0	30	3	< 1
Nervous system disorders						
Peripheral sensory neuropathy	47	5	0	38	6	< 1
Respiratory, thoracic and mediastinal disorders						
Cough[d]	27	0	0	14	0	0
Dyspnea[e]	21	4	0	11	1	0

Key: D=daratumumab, Vd=bortezomib-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.
[b] edema peripheral, edema, generalized edema, peripheral swelling
[c] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection
[d] cough, productive cough, allergic cough
[e] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment are listed in Table 4.

Table 4: Treatment-emergent hematology laboratory abnormalities in Study 4

	DVd (N=243) %			Vd (N=237) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Anemia	48	13	0	56	14	0
Thrombocytopenia	90	28	19	85	22	13
Neutropenia	58	12	3	40	5	<1
Lymphopenia	89	41	7	81	24	3

Key: D=Daratumumab, Vd=bortezomib-dexamethasone.

Monotherapy

The safety data reflect exposure to DARZALEX in 156 adult patients with relapsed and refractory multiple myeloma treated with DARZALEX at 16 mg/kg in three open-label, clinical trials. The median duration of exposure was 3.3 months (range: 0.03 to 20.04 months). Serious adverse reactions were reported in 51 (33%) patients. The most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%).

Adverse reactions resulted in treatment delay for 24 (15%) patients, most frequently for infections. Adverse reactions resulted in discontinuations for 6 (4%) patients.

Adverse reactions occurring in at least 10% of patients are presented in Table 5. Table 6 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥10%.

Table 5: Adverse reactions with incidence ≥10% in patients with multiple myeloma treated with DARZALEX 16 mg/kg

	DARZALEX 16 mg/kg N=156		
	Incidence (%)		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Infusion reaction[a]	48	3	0
General disorders and administration site conditions			
Fatigue	39	2	0
Pyrexia	21	1	0
Chills	10	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	21	0	0
Nasal congestion	17	0	0
Dyspnea	15	1	0
Musculoskeletal and connective tissue disorders			
Back pain	23	2	0
Arthralgia	17	0	0
Pain in extremity	15	1	0
Musculoskeletal chest pain	12	1	0
Infections and infestations			
Upper respiratory tract infection	20	1	0
Nasopharyngitis	15	0	0
Pneumonia[b]	11	6	0
Gastrointestinal disorders			
Nausea	27	0	0
Diarrhea	16	1	0
Constipation	15	0	0
Vomiting	14	0	0
Metabolism and nutrition disorders			
Decreased appetite	15	1	0
Nervous system disorders			
Headache	12	1	0
Vascular disorders			
Hypertension	10	5	0

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see below.
[b] Pneumonia also includes the terms streptococcal pneumonia and lobar pneumonia.

Table 6: Treatment emergent Grade 3-4 laboratory abnormalities (≥10%)

	Daratumumab 16 mg/kg (N=156)		
	All Grade (%)	Grade 3 (%)	Grade 4 (%)
Anemia	45	19	0
Thrombocytopenia	48	10	8
Neutropenia	60	17	3
Lymphopenia	72	30	10

Infusion Reactions

In clinical trials (monotherapy and combination treatments; N=717) the incidence of any grade infusion reactions was 46% with the first infusion of DARZALEX, 2% with the second infusion, and 4% with subsequent infusions. Less than 1% of patients had a Grade 3 infusion reaction with second or subsequent infusions.

The median time to onset of a reaction was 1.5 hours (range: 0.02 to 72.8 hours). The incidence of infusion modification due to reactions was 41%. Median durations of infusion for the 1st, 2nd and subsequent infusions were 7.0, 4.3, and 3.5 hours respectively.

Severe (Grade 3) infusion reactions included bronchospasm, dyspnea, laryngeal edema, pulmonary edema, hypoxia, and hypertension. Other adverse infusion reactions (any Grade, ≥5%) were nasal congestion, cough, chills, throat irritation and vomiting.

Herpes Zoster Virus Reactivation

Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. In monotherapy studies, herpes zoster was reported in 3% of patients. In the randomized controlled combination therapy studies, herpes zoster was reported in 2% each in the

DRd and Rd groups respectively (Study 3) and in 5% versus 3% in the DVd and Vd groups respectively (Study 4).

Infections

In patients receiving DARZALEX combination therapy, Grade 3 or 4 infections were reported with DARZALEX combinations and background therapies (DVd: 21%, Vd: 19%; DRd: 28%, Rd: 23%). Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. Discontinuations from treatment were reported in 3% versus 2% of patients in the DRd and Rd groups respectively and 4% versus 3% of patients in the DVd and Vd groups respectively. Fatal infections were reported in 0.8% to 2% of patients across studies, primarily due to pneumonia and sepsis.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, none of the 111 evaluable monotherapy patients, and 1 (0.4%) of the 234 combination therapy patients, tested positive for anti-daratumumab antibodies. This patient administered DARZALEX as combination therapy, developed transient neutralizing antibodies against daratumumab. However, this assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. Therefore, comparison of the incidence of antibodies to daratumumab with the incidence of antibodies to other products may be misleading.

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding[1] *[see References]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, consider other methods to evaluate the depth of response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no human data to inform a risk with use of DARZALEX during pregnancy. Animal studies have not been conducted. However, there are clinical considerations *[see Clinical Considerations]*. 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.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause fetal myeloid or lymphoid-cell depletion and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematology evaluation is completed.

Data

Animal Data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. In cynomolgus monkeys exposed during pregnancy to other monoclonal antibodies that affect leukocyte populations, infant monkeys had a reversible reduction in leukocytes.

DARZALEX® (daratumumab) injection

Lactation

Risk Summary

There is no information regarding the presence of daratumumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for DARZALEX and any potential adverse effects on the breast-fed child from DARZALEX or from the underlying maternal condition.

Females and Males of Reproductive Potential

Contraception

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of DARZALEX treatment.

Pediatric Use

Safety and effectiveness of DARZALEX in pediatric patients have not been established.

Geriatric Use

Of the 156 patients that received DARZALEX monotherapy at the recommended dose, 45% were 65 years of age or older, and 10% were 75 years of age or older. Of 561 patients that received DARZALEX with various combination therapies, 40% were 65 to 75 years of age, and 9% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients *[see Clinical Studies (14) in Full Prescribing Information].*

OVERDOSAGE

The dose of DARZALEX at which severe toxicity occurs is not known.

In the event of an overdose, monitor patients for any signs or symptoms of adverse effects and provide appropriate supportive treatment.

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PATIENT COUNSELING INFORMATION

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

Infusion Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion reactions:

- itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing *[see Warnings and Precautions and Adverse Reactions].*

Neutropenia

- Advise patients that if they have a fever, they should contact their healthcare professional *[see Warnings and Precautions and Adverse Reactions].*

Thrombocytopenia

- Advise patients to inform their healthcare professional if they notice signs of bruising or bleeding *[see Warnings and Precautions and Adverse Reactions].*

Interference with Laboratory Tests

Advise patients to inform healthcare providers including blood transfusion centers/personnel that they are taking DARZALEX, in the event of a planned transfusion *[see Warnings and Precautions and Drug Interactions].*

Advise patients that DARZALEX can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response *[see Warnings and Precautions and Drug Interactions].*

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HEALTH IT

Why Oncologists Need Technology to Succeed in Alternative Payment Models

Brenton Fargnoli, MD; Ryan Holleran; and Michael Kolodziej, MD

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continued from cover

Prior to the initiation of the current value-based care pilots, there were essentially no oncology practices succeeding in all 3 areas, and few have yet to address any single challenge efficiently. In order to successfully participate in the variety of payment models available to them, practices must consider whether they will formulate an organic solution or seek external support.

With respect to the administrative challenges, manual processes are a feasible solution, but the additional labor can prove costly and inefficient. Technological solutions, particularly solutions that are integrated into practice management and physician workflow, offer an efficient and comprehensive approach to a daunting task. Given the scale of the OCM, the administrative challenges of this model are an excellent case study of how technology might be applied and would even be necessary.

The Challenge of Value-based Arrangements With Multiple Payers

A majority of practices that are in value-based arrangements, including the OCM, use a fairly sophisticated practice management system and electronic health record (EHR). Even with these tools, the diversity of the patient population creates challenges because practices in these arrangements provide service to many payers. Patients with healthcare coverage through these payers all have different benefit plan designs, and it is common for commercial payer projects to only apply to a subset of all patients (most typically, the fully insured population). Even in the simplest case, Medicare fee-for-service beneficiary eligibility for the OCM features an extensive list of inclusion and exclusion criteria,[1] which can be identified by the practice management system but are routinely invisible to the provider at the point of care. Beneficiary eligibility also requires the initiation of therapy with a specific list of both intravenous (IV) and oral agents, with attribution occurring specifically on the date of IV administration or pharmacy dispensing, and then continuing for up to 6 months per episode. Therefore, optimal patient capture would require information exchange between the practice management system and the EHR to verify and document enrollment in a specific value-based program, as well as a mechanism that can track progress through an episode and link the clinical services to billing and collection of applicable management fees. This is certainly achievable through manual processes but clearly lends itself to a technological solution. Flatiron Health offers one such solution to practices utilizing its EHR, OncoEMR.

Flatiron created and applied logic to OncoEMR and practice management data, based on OCM eligibility rules, which helps identify and surface OCM-eligible patients at the practice (**Figure 1**). These analytics are run on a daily basis in near real-time to track patients who are in an OCM episode or about to enter an episode. In order to identify OCM patients at the point of care, Flatiron built a bridge between its analytics layer and OncoEMR to push the OCM eligibility determinations directly to the patient header in OncoEMR.

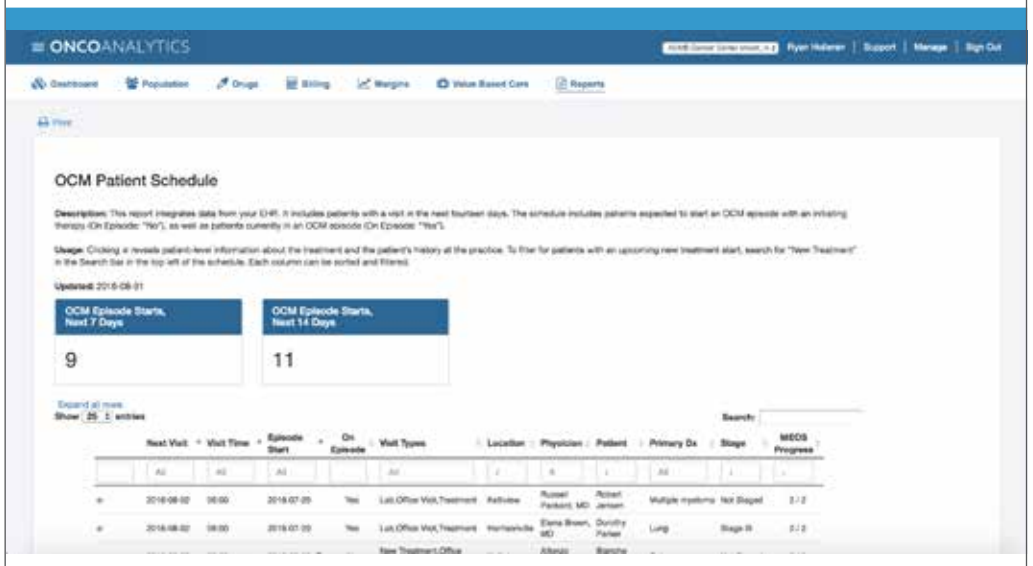
The Institute of Medicine (IOM, now called The National Academies of Science, Engineering, and Medicine)'s 13-point care plan[2] represents an established and widely accepted standard for documenting communication between oncologists and their patients, as well as among treating physicians to facilitate coordination of care. Despite the consensus that there is value in this document, which ensures the care team and the patient are on the same page, numerous practical issues have hampered implementation. Although most, if not all, elements are routinely documented in the course of care, this is rarely done in an organized fashion in a specific location in the EHR. Oncologists are understandably rarely willing to devote time to such additional documentation, and there is no standard physical format that oncologists can access to share this data with patients and other physicians.

Using a Cross-Collaborative Team

While the OCM has mandated that this care plan be completed for every patient enrolled in the program, it is certainly possible to manually complete all 13 elements. However, given that many of these elements exist in other locations in the EHR, a more elegant and more efficient solution is to electronically pull these data into a single structured document that is fully integrated in the EHR.

Flatiron built a 13-point care plan directly within OncoEMR to the IOM's specifications (**Figure 2**). Initially, Flatiron's designers and medical oncologists consolidated these 13 points into 9 discrete sections. Then, to avoid duplicating the data, engineers mapped structured data entered in the clinical workflow to the relevant sections of the care plan. When these fields were absent from the structured clinical workflow, such as prognosis and estimated cost, medical oncologists and

FIGURE 1. Eligible Patient Identification and Tracking



Flatiron's OCM Patient Schedule and Tracker help practices identify OCM-eligible patients, which facilitates appropriate onboarding and care coordination, and tracks patients throughout their 6-month episodes. The reports identify eligible patients based on OCM inclusion and exclusion criteria, and then display patients who are already in an episode or are likely to enter an episode in the next 2 weeks. The reports are interactive, searchable, and printable to allow users to efficiently share the population of interest.

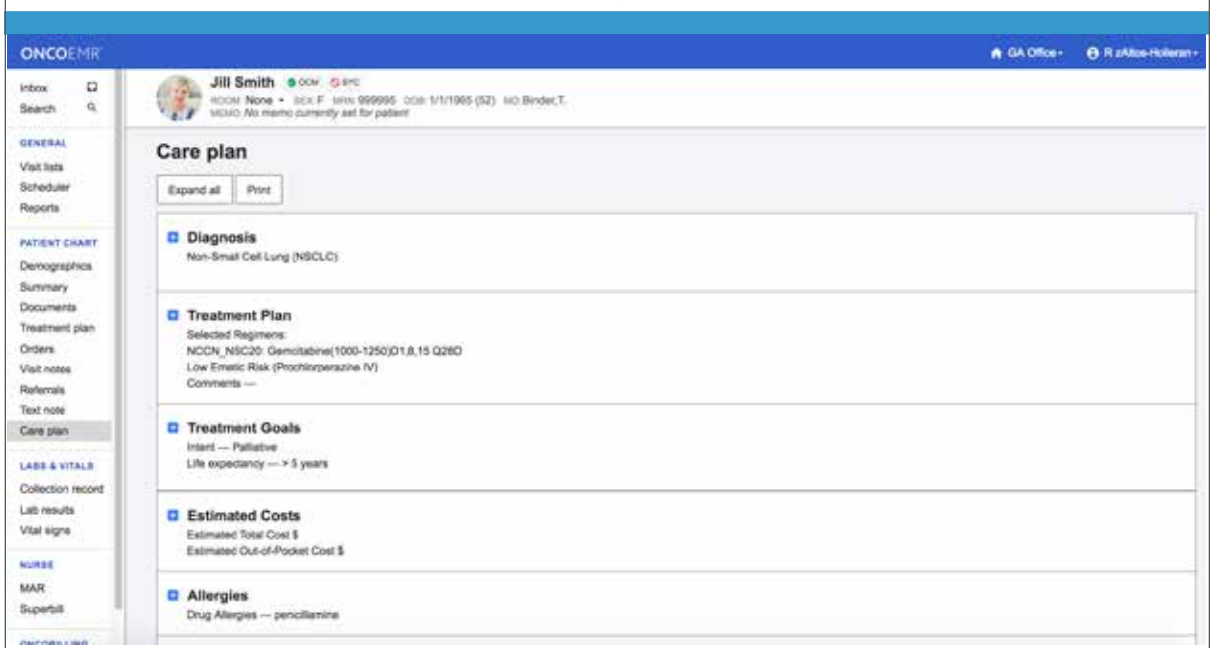
OCM indicates Oncology Care Model.

medical informaticists were brought in to create appropriate data fields within the care plan page. Next, the medical oncology and communications teams crafted patient-facing language, which would surface based on the data fields that were documented. Throughout this cross-functional collaboration, the design and product management teams continued to perform user research and worked to ensure a quick and intuitive user experience.

Finally, for some time, payer contracts have required reporting of quality metrics. As an example, most practices participated in Physician Quality Reporting System; however, the scale of this reporting has been massively expanded—initially by the OCM and subsequently by the Merit-based Incentive Payment System (MIPS), under the Medicare Access and CHIP Reauthorization Act. There are now more measures, reporting is more frequent, and we foresee that patient level detail will ultimately be a requirement. The existing list of required quality metrics reporting may not seem daunting until one begins to understand and execute the precise logic required to identify eligible patients and document physician performance on these measures. While the required processes to report have been precisely defined by the Center for Medicare & Medicaid Innovation (CMMI) as part of the OCM, several of these steps are open to interpretation. In the absence of a consistent process for applying these rules, errors will be inevitable. Since the consequence of "getting it wrong" is either a reduction in savings generated in the OCM or an outright fee schedule penalty under MIPS, there is a strong incentive to "get it right."

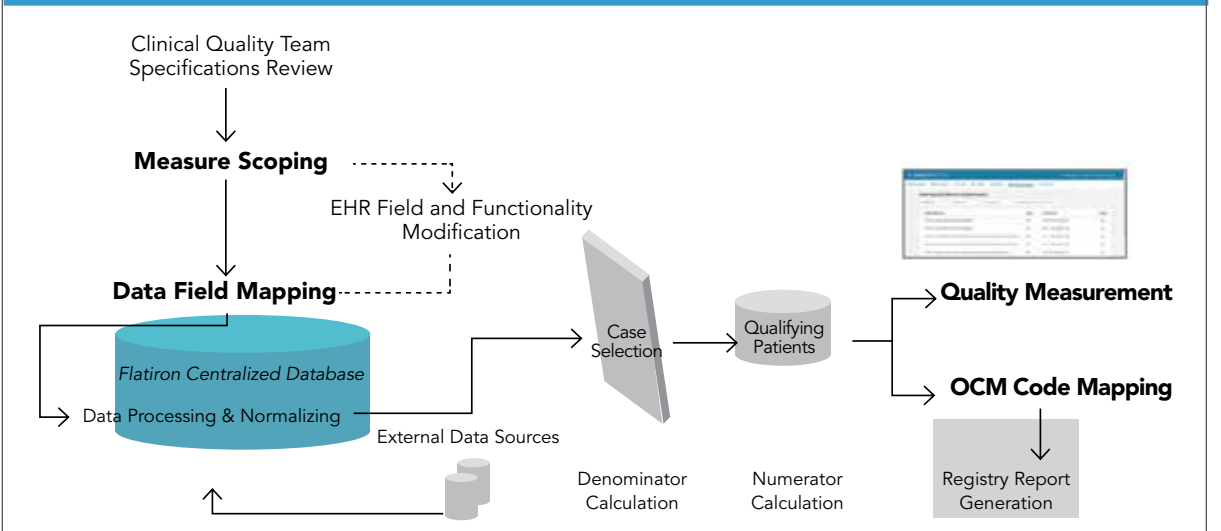
The data required to report the quality measures can be in structured fields in the EHR, which makes the ability to automate reporting an obvious advantage. In fact, given the complexity of the processes involved in calculating these measures, the ability to iterate on these measures to guarantee optimal performance makes a technological solution far superior to a manual solution. In addition, the results can be used to populate a dashboard, visible to providers as a process improvement tool.

FIGURE 2. 13-Point Institute of Medicine Care Management Plan



Providers can seamlessly document a care plan directly in OncoEMR that includes the 13 components of the Institute of Medicine Care Management Plan. Using data sourced from OncoEMR, these care plans reduce additional manual data entry and manipulation. There is a field corresponding to each of the 13 points. For fields not routinely completed elsewhere in OncoEMR, care teams can utilize a drop down menu or free text. All fields can be customized to meet the needs of the individual patient. When completed, the care plan can be sent to co-managing providers or printed for the patient in patient-facing language.

FIGURE 3. Quality Measure Scoping and Data Processing



Flatiron's quality measure scoping and data processing methodology involves the clinical quality team, made up of oncologists, advanced practitioners, and engineers, reviewing measure specifications, advising on OncoEMR configurations, designing integrated workflows, and maintaining the integrity of quality measurement. Ultimately, this enables the data captured throughout clinical workflows to be translated into meaningful insights in the form of a patient-level performance dashboard and automated reports that can be used to submit data to the registry.

Automated Quality Measurement

To automate quality measurement, Flatiron's quality team of medical oncologists, quantitative scientists, and data insights engineers first scoped and documented the logic needed to calculate the numerator and denominator of each OCM quality measure from the information available within OncoEMR. These data points were then mapped within OncoEMR. Structured fields were created for data points that did not previously have them. These data elements were then harmonized, normalized, and mapped back to Flatiron's centralized database to create an analytics-ready dataset. With this dataset, Flatiron built logic to calculate the OCM quality measures (**Figure 3**). Following quality assurance and control, visualization of these quality measurements were built and deployed to OCM practices across 18 states.

Early Results and Lessons from the First 6 months of the OCM

Flatiron's technological solution has been available to practices using OncoEMR since the start of the OCM (July 2016). With OncoEMR practices comprising nearly 30% of the OCM, initial results of these practices offer interesting insight into implementation and performance. In reviewing the first 6 months (July 1, 2016, to December 31, 2016) of the OCM across 32 practices, we observed 15,705 patients enrolled in the OCM and 5290 care plans completed and distributed to patients. In reviewing financial data for 20 OCM practices during the same time period, we found that these practices received Monthly Enhanced Oncology Services »

KOLODZIEJ

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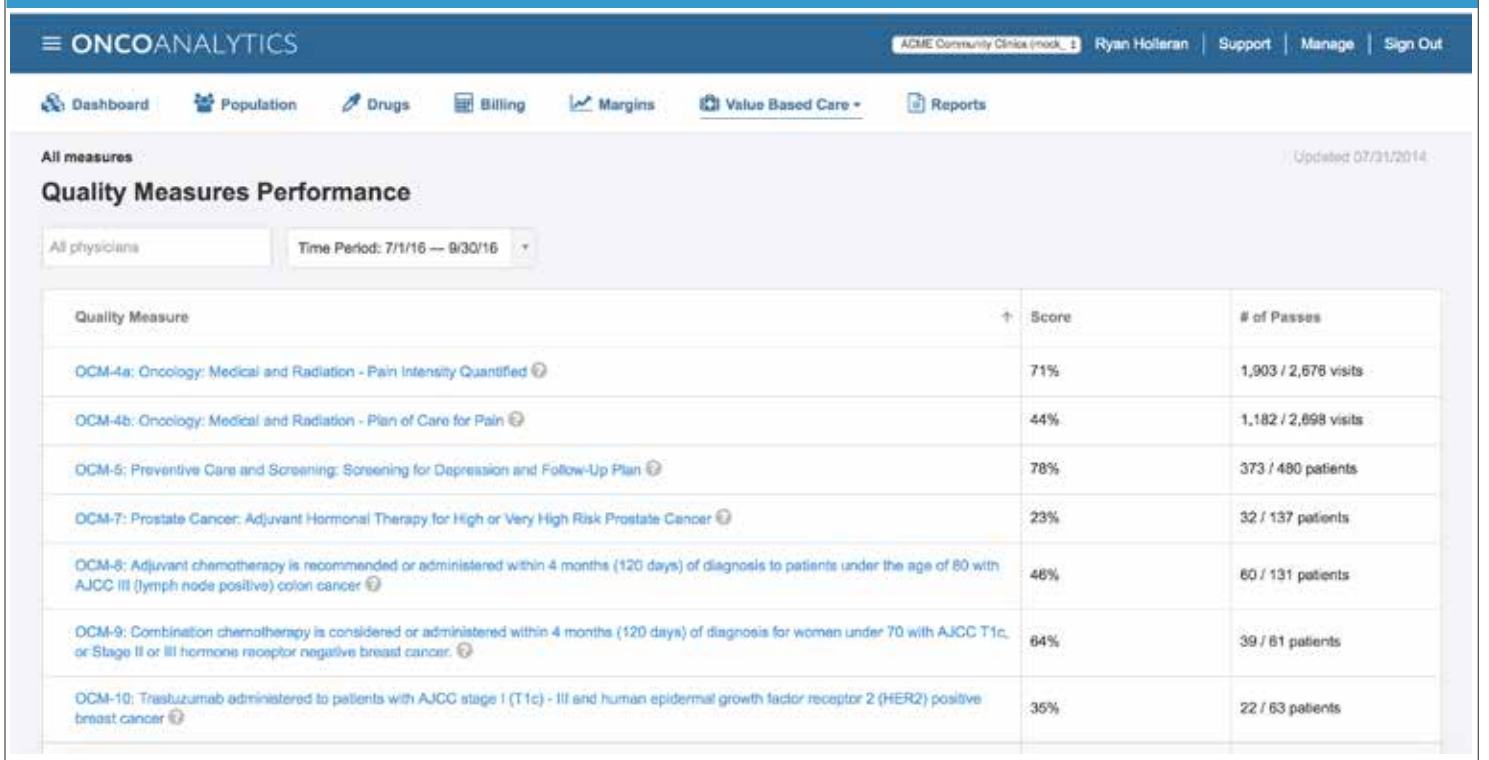
FIGURE 4. Quality Measure Dashboard



Flatiron's quality measure dashboard allows practices to gain near real-time insight into their OCM quality measure performance. Flatiron's OncoEMR workflows integrate structured data field capture for all practice-reported OCM quality measures. Quality data are captured throughout each care team member's regular workflow. Flatiron then processes these data elements to create a comprehensive dataset, and applies logic defined by Flatiron's quality team, consistent with OCM technical specifications, to generate quality measurement calculations and performance reports. Each report displays quality measure performance data by physician and patient within the reporting period for which a practice is currently being measured. Patient-level data is provided to clearly display patients who have passed or failed a measure, and to point out incomplete documentation.

THE DATA REQUIRED TO REPORT THE QUALITY MEASURES CAN BE IN STRUCTURED FIELDS IN THE ELECTRONIC HEALTH RECORD, WHICH MAKES THE ABILITY TO AUTOMATE REPORTING AN OBVIOUS ADVANTAGE.

(MEOS) payments averaging a projected $66,673 per medical oncologist per year in the OCM. Based upon these practices' OCM patient volume, only about half of their MEOS revenue potential was realized during this time period.

The results described offer several important lessons. Even with a near comprehensive technological solution for the administrative burden of the OCM, implementation and adoption of new tasks and care processes take time and effort. It involves,

- Staff training
- Hiring new staff
- Modifying physician workflow

These changes cannot be implemented spontaneously. Rather, they would need performance measurements and, where necessary, improvements. Strong executive and physician leadership are vital for the success of all elements of value-based care, but the clear advantages to identifying and co-developing a strategy with a technology partner will make this transition—one for which few practices are currently configured to execute—smoother and much more successful. This will allow practices to focus on the even more challenging elements of care delivery reform. As payers contemplate their goals in value-based care, they must consider the tools available to practices in order to minimize the likelihood that the burdens associated with executing multiple models are so onerous that box-checking gets in the way of real transformation. Patients' lives are at stake. ◆

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PHYSICIAN PERSPECTIVE

Making Sense of Advanced Payment Models

Barbara McAneny, MD; Stephen S. Grubbs, MD; Walter Birch, MBA; Dan Sayam Zuckerman, MD

continued from cover

- The second track promotes payment through advanced Alternative Payment Models (APMs).[1]

Under MIPS, which consolidates 3 separate programs, physicians report on:

- Quality (formerly the Physician Quality Reporting System or PQRS)
- Cost/resource use (formerly the Value-Based Modifier program)
- Advancing care information (formerly Meaningful Use)
- Improvement activities

Physician and practice performance in 2017 will be analyzed in 2018, and adjustments to the physicians' fee schedules will be released in 2019. Physicians may report individually or as an entire practice, and scores will be based upon reported activities and ranked against all others who report under MIPS. Physicians or practices that rank ahead of their peers will be eligible for a fee schedule increase of up to 4% in 2019, and those ranked behind their peers face a decrease in their fee schedule of up to 4% in 2019. The potential fee schedule gain or loss will witness an annual increase to 9% in 2022.[2]

The good news is that CMS has deemed 2017 as a preparation and transition year (termed "Pick Your Pace"); a physician can avoid the 4% reduction from MIPS in 2019 by reporting 1 measure for only 1 patient for the entire year.

Advanced Alternative Payment Models

The QPP encourages physicians and practices to participate in APMs, including those designated by CMS as "advanced APMs," characterized by the Office of the National Coordinator for Health Information Technology–-certified electronic health record (EHR) use, quality reporting, and financial standards that require 2-sided financial risk. Participation in an advanced APM that provides care for a threshold quantity of patients exempts physicians and practices from the MIPS program and provides an annual 5% reimbursement bonus starting in 2019.

The Center for Medicare & Medicaid Innovation (CMMI)'s Oncology Care Model (OCM) qualifies as an advanced APM if a practice elects the 2-sided financial risk option. This advanced APM option is limited to the nearly 200 oncology practices that were accepted into the OCM program and, subsequently, chose to participate.

Because the MACRA legislation specifies that CMS should review physician-sponsored APM models for Medicare reimbursement, Medicare has established the Physician-Focused Payment Model Technical Advisory Committee (PTAC). PTAC will evaluate the proposed models based upon their attributes of value-based care and reimbursement that will qualify as an advanced APM. One such APM is the Patient-Centered Oncology Payment Model (PCOP) developed by the American Society of Clinical Oncology (ASCO).

Patient-Centered Oncology Payment Model

Several years before MACRA, ASCO volunteers foresaw the need for a payment model that compensated oncologists for providing oncology care in a high-quality, patient-centered fashion, rather than in the current volume-based manner. The concept includes reimbursing oncology professionals for performing high-value care improving activities that had not been compensated previously.

ASCO mobilized a task force of oncologists, staff, and consultants to develop the model. The volunteer oncologists were geographically diverse and represented a variety of practice settings, including independent practice, academic institutions, and health system employed practice. This task force identified services that promote lower costs and higher quality care performed during an episode of chemotherapy or immunotherapy that are currently uncompensated or undercompensated, including:

- Detailed treatment planning
- Patient education
- Case management

Analyses of the cost of a course of chemotherapy/immunotherapy were performed to identify costs that could be eliminated or reduced. The task force then developed a payment mechanism for oncology care providers that would allow them to pay for the practice transformation needed to provide the enhanced valued care.

These efforts led to the creation of the PCOP model, published in May 2015.[3] The model encompasses a chemotherapy or immunotherapy episode of care with 3 levels of reimbursement, leading from basic fee-for-service care to monthly payments to overall care bundles.

Level 1 is based on the concept of adding 3 additional reimbursement codes to cover the enhanced practice services:

- An upfront new patient treatment planning code applied at the start of a new episode of chemotherapy
- A monthly case management code during the course of chemotherapy
- A monthly posttherapy case management code for up to 6 months of monitoring following chemotherapy

A proposed fourth code would support clinical trial management. These codes augment the current evaluation and management codes, and this additional compensation will allow the physician to plan the full course of therapy, educate the patient and family, and fund practice services to efficiently manage treatment and post-treatment complications and toxicities. Examples of enhanced services include staff nurse triage lines, standardized triage protocols, extended office hours, »

THE [PCOP] MODEL ENCOMPASSES A CHEMOTHERAPY OR IMMUNOTHERAPY EPISODE OF CARE WITH 3 LEVELS OF REIMBURSEMENT.

ASCO
American Society of Clinical Oncology

MCANENY

GRUBBS

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and practitioner and infusion center capacity for same-day service to avoid emergency department (ED) and hospital admission. The model also requires adherence to care quality measures and appropriate care and resource use such as ASCO's Choosing Wisely measures.[4]

The PCOP model achieves 2-sided financial risk by adjusting reimbursement to quality and performance targets. ASCO financial modeling has demonstrated both an increase in practice revenue and an overall cost saving to payers while enhancing care quality. Modeling of a typical episode of chemotherapy on a Medicare fee schedule increases Part B non-drug revenue to the practice by nearly 50% (4.3% of total cost) while simultaneously decreasing the overall cost of care by 4%.

Levels 2 and 3 of PCOP are for the more advanced practices that have shown they can successfully manage the cost of care for their patients. In level 2, monthly payments are made in lieu of all physician billings, including the 3 new codes described above and the optional clinical trials management code. Payments would have to be negotiated by disease state and risk adjusted. Finally, in level 3, bundled payments would be paid for the entire course of therapy, but they would have to be negotiated by disease state and risk adjusted. Bundling of payments that include chemotherapy and other drugs are complex and would have to be continually updated to account for new therapies.

PCOP is designed to benefit patients and their families with accurate diagnosis and appropriate treatment, education and support services, less ED and hospital care, and financial benefit by reduction of expensive ED and hospital care and unnecessary drugs and tests. Oncology practices will benefit from increased revenue from the new codes, which will reimburse the practice for current nonbillable or undercompensated services that promote effective care management and fund practice transformation—this will allow all members of the oncology care team to perform at the highest level of their license and skill set. Payers will benefit from not just lower costs, but enhanced quality of care and member satisfaction.[5]

Oncology Medical Home Model Shows Promise

Physician practices that move from "volume-based" to "value-based" payment models require adjustments of their practice to be successful. Published evidence suggests that physician practice transformation to an oncology patient-centered medical home model will achieve the goals of better care and cost required by an APM.[1] A CMMI grant–funded COME HOME project, which incorporated oncology medical home systems within 7 oncology practices and measured oncology practice outcomes, demonstrated high quality care at reduced costs and high patient satisfaction. Over the 3-year period, ED use at the 7 practices decreased by 11.7%, hospital admissions declined by 6.6%, and hospital readmissions reduced by 12.5%. These cost-saving results were achieved with a high patient satisfaction of 98.1%.[6] The tools that were developed and the knowledge that was acquired from this project reside in Innovative Oncology Business Solutions (IOBS).

ASCO has licensed the IOBS tools to assist practices in the transformation required to be successful in this new era of practice. This initiative, named the ASCO COME HOME program, will assist practices in implementing the programs necessary to acquire and develop medical oncology home characteristics that will promote success in APMs.

The PCOP model, which can be adapted by commercial payers and by Medicare, is currently operational with an independent oncology practice and a regional commercial insurer. Several other practices and commercial insurers are evaluating the model for implementation. The PCOP model is also being revised to be presented to the PTAC and then CMS for designation as an advanced APM. The following revisions are planned:

- Quality metrics to ensure cost savings while delivering appropriate care, and an efficient reporting of quality metrics that will not be an onerous requirement on physicians.
- Incorporating nationally accepted pathways into the model to ensure that patients receive evidence-based treatment.
- A 2-sided financial risk model that rewards outstanding care and penalizes less than optimal care, with a level of downside risk that will not lead to the insolvency of physician practices.
- EHR utilization and reporting.
- Oncology medical home infrastructure requirements.

ASCO is hopeful that PCOP will be accepted by CMS as an advanced APM and become available to medical oncologists as an alternative to the MIPS program.

Conclusion

Value-based healthcare is an evolving practice reality accelerated by the QPP, And APMs seem the likely predominant payment model of the future in this new system. ASCO's PCOP model will offer oncology practices an APM that will provide improved patient care and satisfaction, reward physicians for providing excellent care, and reduce costs for patients and payers. The ASCO COME HOME program will assist oncologists and practices in this transformation of care, and with PCOP, will attempt to achieve the healthcare Quadruple Aim (enhanced patient experience, improved population health, cost reduction, and improved provider work life). ◆

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