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ALSO IN THIS ISSUE

Doing More for More Patients



A PREVIVOR'S STORY



Amy Byer Shainman has a family history of mutations in the BRCA gene and cancer, and she is BRCA1 positive. In this excerpt from her upcoming book, Shainman, a patient advocate,

emphasizes the importance of genetic counseling and shares her decision to undergo prophylactic surgery to reduce her risk of developing cancer (SP241).

COLLABORATION, THE FOUNDATION OF CARE TRANSITIONS



Care providers from New York Oncology and Hematology describe the implementation of a collaborative care model, which brings together clinical care providers, social workers, and the family to improve patient experience throughout the cancer care continuum (SP248).



CONFERENCE COVERAGE

NCCN
Coverage of the 22nd Annual Conference of the National Comprehensive Cancer Network (NCCN) held in Orlando, Florida, includes NCCN Guideline updates and sessions that discussed disparity and cancer care access barriers (SP251).

COA

At the 2017 Community Oncology Alliance Conference, sessions and presentations steered attendees through the complex world of CMS' Oncology Care Model, adequate use of a learning health system, coping with rising drug prices, and more (SP259).

PROVIDER PERSPECTIVE

Project ECHO: An Effective Means of Increasing Palliative Care Capacity

Sanjeev Arora, MD; Tracy Smith, BS; Jennifer Snead, PhD; Sarah Zalud-Cerrato, MPH; Lisa Marr, MD; Max Watson, MBChB; Sriram Yennu, MD; Amy Bruce, MPP; Chris Piromalli, DO; Stacy Kelley, MPH; Nandini Vallath, MD; Gabriela Píriz, MD; Gabriel Sehabiaga, MD; and Alvaro Méndez, MD

INTRODUCTION

Globally, the need for integrated palliative care has never been greater. Populations are aging, and rates of terminal non-communicable diseases continue to progress. Approximately half of all patients with cancer, for example, will eventually succumb to their disease—nearly one-third of cancer deaths happen within 6 months of diagnosis.¹ Organizations, such as the National Academies of Science, Engineering, and Medicine (formerly Institute of Medicine) and the American Society of Clinical Oncology, recommend full integration of palliative care as a routine component of comprehensive cancer care.² Integrated palliative care—which encompasses coordination of care for multiple severe, complex conditions; behavioral health concerns;

PAYER PERSPECTIVE

The Carrot or the Stick? Integrating Palliative Care Into Oncology Practice

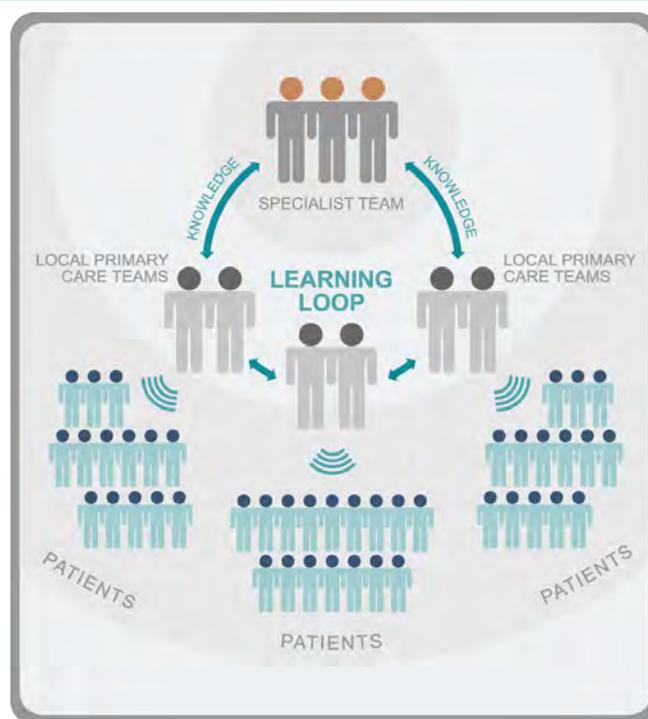
Torrie K. Fields, MPH

IN AN ERA WITH INCREASED EMPHASIS on bending the cost curve while increasing availability of targeted therapies for those with cancer, it can be difficult to strike the right balance between the art and the science of practicing high-quality oncology care. Perhaps just as difficult is the role of a regulating body or healthcare financier in providing the right incentives, policies, and authorization practices that allow clinical judgment while ensuring treatments are of high quality, evidence-based, and align with patient preferences. As cancer interventions become more effective and more complex, it is essential to create guardrails and incentives so that high-quality, patient-centered, cost-effective healthcare continues to be delivered.

Integrating palliative care into a treatment plan, preferably at the point of diagnosis, is crucial to delivering high-quality cancer care. Palliative care—which focuses on relieving the pain, symptoms, and stresses of a serious illness—has the ability to change the delivery and experience of healthcare for patients and caregivers. Many prospective studies have shown

CONTINUED ON SP277

FIGURE 1. Project ECHO-Model: The ECHO Model Moves Knowledge, Not Patients



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PHARMACIST'S ROLE

Transitions of Care in Patients With Cancer

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

Introduction

While on the one hand healthcare is constantly evolving with new technology, medical advances, policy changes, and reimbursement strategies, on the other hand, the cost of avoidable readmissions or preventable adverse events (AEs) are burdening the healthcare system. Jencks and colleagues concluded that about 20% of Medicare patients were readmitted within 30 days, with about 50% of the 20% who were readmitted having no follow-up post discharge.¹

CONTINUED ON SP280

SUPPORTING YOUR PATIENTS FROM THE START

We're committed to providing streamlined services for your patients. That's why we created KISQALI Care, a comprehensive support program that assists eligible patients throughout their treatment with KISQALI® (ribociclib).



1 FREE Treatment Cycle of KISQALI and/or FEMARA

All patients can receive a free 1-treatment cycle supply of KISQALI and/or FEMARA® (letrozole) (including generic letrozole).*



KISQALI 5-Treatment Cycle Access Program

Patients with commercial insurance who are still waiting for their coverage to take effect for KISQALI may be eligible for an additional supply of medication that could continue for up to 5 treatment cycles.†



KISQALI Care Patient Navigator

Eligible patients will be connected with a dedicated navigator who can help them understand insurance coverage, identify potentially available financial resources, and schedule routine monitoring tests through the KISQALI Care @ Home Monitoring program.

*This offer is available for patients with a valid prescription for KISQALI and/or FEMARA (including generic letrozole), including for patients who have not been prescribed KISQALI or another Novartis product.

† Limitations apply. Eligible patients must have commercial insurance, a completed Service Request Form, and be experiencing a delay in obtaining coverage for KISQALI. Program is not available to patients whose medications are reimbursed in whole or in part by Medicare, Medicaid, Tricare, or any other federal or state program. No purchase necessary. Participation is not a guarantee of insurance coverage. Once coverage is approved, patients will no longer be eligible. Novartis Pharmaceuticals Corporation reserves the right to rescind, revoke, or amend this Program without notice.

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.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

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



KISQALI and/or FEMARA \$0 Co-Pay

Patients may be eligible for immediate co-pay savings on their next prescription[†]:

- Commercially insured patients pay \$0 per month
- Novartis will pay the remaining co-pay, up to \$15,000 per calendar year, per product
- This offer is available for patients with a valid prescription for KISQALI and/or FEMARA (including generic letrozole), including for patients who have not been prescribed KISQALI or another Novartis product



Convenient ECG Monitoring

- **KISQALI Care @ Home Monitoring** allows eligible patients to receive their ECG monitoring and bloodwork performed by an experienced medical professional in the comfort of their own homes[§]
- **KISQALI Care In-Office Monitoring** can provide you with ECG testing equipment so you can perform monitoring right in your office

[†] Limitations apply. Patient must have commercial insurance. Offer is not valid under Medicare, Medicaid, or any other federal or state program. Novartis reserves the right to rescind, revoke, or amend this program without notice. For full terms and conditions, visit www.CoPay.NovartisOncology.com or call 1-877-577-7756.

[§] Limitations apply. KISQALI Care @ Home Monitoring is not available to patients with Medicare, Medicaid, or any other federal or state program, or residents of Michigan, Minnesota, or Rhode Island. Novartis reserves the right to terminate or modify this program at any time.



For more information, visit www.KISQALI.com/Access.

IMPORTANT SAFETY INFORMATION (continued)

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.



IMPORTANT SAFETY INFORMATION (continued)

Avoid the use of KISQALI® (ribociclib) 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 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.

Embryofetal 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 embryofetal 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 $\geq 20\%$) 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 $\geq 20\%$) 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%).

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)

Adverse drug reactions	KISQALI + letrozole N=334			Placebo + letrozole N=330		
	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)

¹abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased

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

Laboratory parameters	KISQALI + letrozole N=334			Placebo + letrozole N=330		
	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 \geq 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 13th 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 \geq 65 years of age and 35 patients (11%) were \geq 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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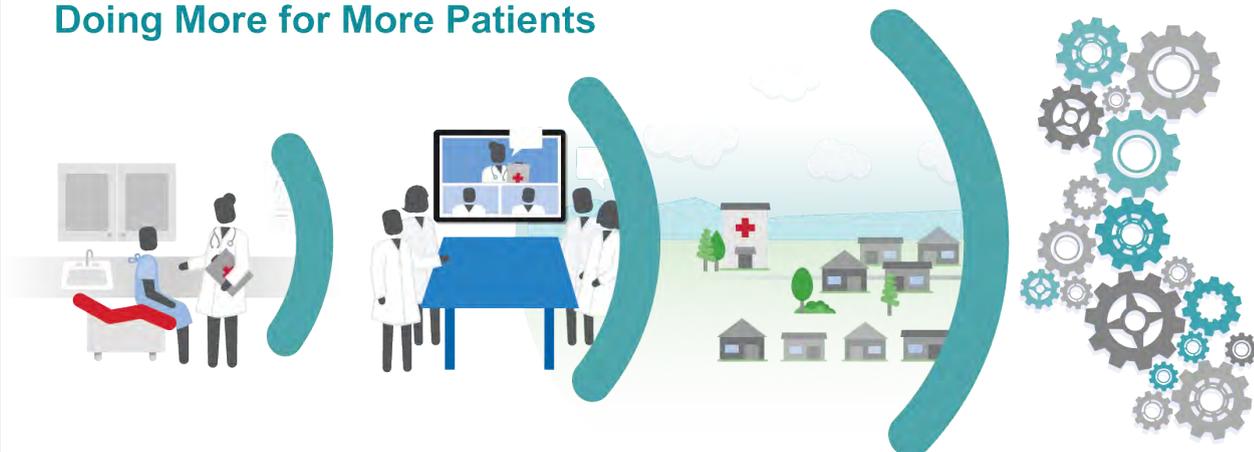
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SPECIAL ISSUE / TRANSITIONS OF CARE

JUNE 2017
VOLUME 23 ISSUE 7

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- Right Place
- Right Time

PROVIDER

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FROM THE CHAIRMAN

Ensuring Adequate Cancer Care, From Diagnosis to Survivorship



MIKE HENNESSY, SR

PATIENT CARE IS A TEAM EFFORT

and is filled with challenges at every step. Often more challenging than the actual care are the communication gaps among providers, which can lead to undesirable outcomes.

Nowhere is this team-based care model more evident than in oncology, where not just the care providers, but the patient and family caregivers are increasingly part of

the decision-making process. However, these care delivery models can fall apart unless there's constant, and consistent, communication and information sharing among the multiple

CARE DELIVERY MODELS CAN FALL APART UNLESS THERE'S CONSTANT, AND CONSISTENT, COMMUNICATION AND INFORMATION SHARING AMONG THE MULTIPLE STAKEHOLDERS.

stakeholders. And as the authors from New York Oncology and Hematology highlight in this issue, the roles played by nonclinical interdisciplinary teams is equally important, as it can impact a patient's care plan, care experience, and overall well-being.

A "navigation team,"

the authors write, can help provide continuity of care over the course of a patient's treatment and ensure that important details are addressed as a patient transitions through the healthcare continuum.

Pharmacists, particularly health-system pharmacists, play a critical role in enhancing transitions of care for patients undergoing cancer treatment via medication reconciliation, education, and postdischarge follow-up. A nurse or a pharmacist can be a helpful "transition coach" for older patients and can help prevent readmissions.

With the integration of palliative care into mainstream medicine, but the dearth of specialists who can provide this kind of care especially in rural areas, healthcare organizations are leveraging technology solutions to ensure patients and care providers can take advantage of the select few experts. Project ECHO, or Extension for Community Health Outcomes, is one such global project. Initiated at the University of New Mexico, Project ECHO now has 110 partners across 20 countries. Through teleECHO clinics, which are videoconference-enabled sessions, specialists share their expertise and community providers share their experience with individual patients via case-based learning and telementoring.

Payers, too, have recognized the value of care collaboration and integrating early palliative care into oncology practice, and are providing incentives through reimbursement models to boost the practice.

We hope you enjoy this summer issue of *Evidence-Based Oncology*™. As always, 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

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The Transition to Integrate Palliation in Cancer Care

Joseph Alvarnas, MD



JOSEPH ALVARNAS, MD

THE NATURE OF A CANCER

diagnosis and subsequent treatment is that patients are not only faced with the challenges of undergoing complex, often intensive, treatments, but also with the many changes in their care setting, providers, ancillary services, and goals of care that may occur over the course of their cancer journey. Unlike diseases like community-acquired pneumonia, in which care is limited to a discreet episode, the longitudinal nature of care needs for patients with cancer requires a different, more comprehensive system of care delivery. This, by necessity, requires that our system deliver care throughout the numerous transitions that our patients experience. High-quality cancer care can only occur when these “transitions in care” are delivered in a prospectively planning, systematic, patient-centered way. There are diverse arrays of transitions of care that mark the cancer care experience: inpatient to outpatient care, pediatric to adult care, therapy with curative intent evolving toward therapy directed towards palliation.

Throughout these transitions of care the stakes for the patient are very high; we have both an opportunity to contribute substantively to the patient-centeredness of care or to undermine the delivery of effective care. In this issue of *Evidence-Based Oncology™ (EBO™)*, we attempt to illustrate some of these episodes of care and highlight the opportunities for improving the effectiveness of care through these transitions.

One example of an immensely important transition of care for patients is that of ensuring the early integration of palliative/supportive care into post-cancer diagnosis treatment planning. However, the early use of palliative care is often a missed opportunity. There is a common misperception that palliative care solutions are only germane to patients at the end-of-life, thus initiation of these services are often delayed until patients are referred for hospice or comfort care services.¹ Cancer patients have an extraordinary number of care needs that are frequently under recognized and therefore unaddressed within our current care delivery system.

The World Health Organization defines palliative care as:

An approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.²

Given the breadth of clinical skills that palliative care physicians can bring to the patient, this set of care services has the ability to complement the skills of the medical oncologist/hematologist in serving unmet patient care needs through treatment and survivorship.

The unique expertise of palliative care physicians can, in fact, help us bring increasingly more patient-centeredness to our care delivery sys-

tem. In a study comparing the impact of an early versus delayed model of palliative care referral for patients with non-small-cell lung cancer, there was no difference in the total number of chemotherapeutic regimens used per patient in either group, but there was a significant improvement for the early consultation group in the use of chemotherapy in the last 60 days of life, a longer interval between the last chemotherapy regimen and death, and a higher proportion of patients who survived for more than 1 week under hospice care.³

Palliative care represents only one of the many opportunities for mindful, value-added care transitions that can enhance the lives of our patients. The idea of carefully aligning expertise and clinical skills, delivered through carefully orchestrated transitions of care, represent a major advance in cancer care. In this issue of *EBO™*, we explore a number of these key opportunities to improve the experience of patients affected by cancer. Sanjeev Arora, MD, and colleagues review the ECHO model of palliative care that brings together primary care physicians and expert specialists for transition-of-care mentoring and communication of best practices. Brandon R. Shank, Phuoc Anh Nguyen, and Emily C. Pherson provide an overview of the role that pharmacists may serve in enhancing the effectiveness of transitions of care for cancer patients in ways that improve medication safety. Amy Byer Shainman shares her experience as a cancer “previvor” in navigating transitions in care for patients who are at high-risk of eventually developing cancer. Finally, Rufus Collea, MD, and colleagues provide their perspective on innovative strategies that can be used to improve palliative care, patient navigation, and interdisciplinary patient-family communication.

How can we ensure that more patients can benefit from effective, early palliative care? Perhaps this involves the breadth of stakeholders who participate in the care of these patients to overcome their prejudices over the word “palliative.” Palliation involves an acknowledgement that a patient’s cancer care needs extend well beyond the need for surgery, chemotherapy, and radiation therapy. In embracing the full range of needs of our patients, including the need to manage the distress associated with a cancer diagnosis, we can continue to bring increasingly effective, patient-centered care to those in need. A partnership between the oncologist and the palliative care physician provides an increasingly robust response to the needs of our patients and their families. ♦

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PATIENT PERSPECTIVE

Do What I Couldn't...and Go Save Your Life

Amy Byer Shainman



AMY BYER SHAINMAN, otherwise known as **@BRCAresponder** on Twitter and social media, educates others about hereditary cancer via many social media platforms and national media placements. As a passionate advocate,

Shainman shares her own BRCA story, offers support, and emphasizes the importance of certified genetic counseling in the genetic testing equation. In 2010, she underwent prophylactic surgeries: an oophorectomy, a hysterectomy, and a nipple-sparing, skin-sparing mastectomy with reconstruction, drastically reducing her cancer risk. Resources and information on BRCA and other hereditary cancer syndromes can be found on her website: thebrcaresponder.blogspot.com.

Seeing a huge void in the hereditary cancer community regarding cancer risk in men, Shainman served as executive producer for the documentary film, *Pink & Blue: Colors of Hereditary Cancer*. The film opened in Los Angeles in 2015 and is now available to watch via iTunes and GooglePlay.

Shainman is also the creator of #HereditaryCancerNews, a digital monthly news compilation, and the co-creator of #GenCSM (Genetic Cancer Social Media, @Gen_CSM), a popular cancer ontology hashtag and Twitter chat. Most recently, she became a member of the National Society of Genetic Counselors' Digital Ambassador program, a group of influencers with unique perspectives and knowledge in the fields of genetics and genetic counseling.

Shainman, who lives in Florida with her husband and children, has chronicled her story as a BRCA1 gene mutation carrier in an upcoming memoir, *Resurrection Lily*, which will be out later this year. These are a few excerpts from her book detailing some of her experiences as a previvor.

**BRCA: The Basics**

Every cell in our body contains 23 pairs of long, thin structures called chromosomes. We inherit 1 chromosome of each pair from our mother, and the other from our father. Most mutations in the BRCA susceptibility genes (BRCA) are inherited from the mother or father, rather than representing new (or de novo) genetic changes. This means that at some point in time, the DNA of a relative changed or mutated and that genetic change has been passed down through the generations.

Our genetic information is stored on our chromosomes in tiny units called genes. We have tens of thousands of genes that help code for everything about our bodies: from eye color to hair color to disease risks. We all have 2 copies of BRCA1, 1 on each of our two #17 chromosomes. A woman who inherits 1 mutation in BRCA1 is at an increased risk of developing both breast and ovarian cancer, while a man who carries a BRCA1 mutation is at an increased risk for breast and prostate cancer. BRCA2 is located on chromosome 13, and we all have 2 copies of this gene. Women with 1 BRCA2 mutation are at an increased risk of developing breast, ovarian, and pancreatic cancer while men who carry 1 BRCA2 mutation are at an increased risk of breast, prostate, and pancreatic cancer.

— Ellen Matloff, MS, CGC, CEO, My Gene Counsel

No one could believe my sister Jan's ovarian cancer was an early stage, contained cancer. How could Gilda Radner's grapefruit-sized ovarian cancer be stage IV and Jan's grapefruit-sized ovarian cancer be stage I? Another surprise was that Jan's final pathology indicated, besides stage IC ovarian cancer, that she also had stage 1B uterine cancer. Her surgeon recommended she undergo 6 rounds of chemotherapy to make sure all the cancer was gone.

A year later, in the fall of 2009, life was slowly getting back to normal for my sister and our family. When Jan found out there was an ovarian cancer conference in Las Vegas, she had a feeling she should go to learn more. Her take-home message from the conference was: "Get genetic testing for B-R-C-A mutations!" Why? Because she learned she had many red flags:

- She was of Ashkenazi Jewish descent
- She had 2 primary cancers at the same time (uterine cancer and ovarian cancer)
- She was younger than 50
- There was a family history of breast cancer on our dad's side of the family

With her newfound knowledge, my sister made an appointment with a certified genetic counselor at the hospital where she was treated.

It turned out that I was BRCA1 positive. All that I could think about was my sister Amy. Then, the genetic counselor informed me that ALL my siblings needed to be tested, not just my sister, but my brothers, too.

— Jan Byer

Although I didn't know exactly what genetic testing would mean for me specifically, I knew that the outcome of my own genetic testing results was going to have an impact on my future. So, I started maintaining a journal, not just for myself, but also for my kids and for future generations of my family. Moreover, I felt in my gut that there was an opportunity for me to help others gain insight from my experience.

As a strong woman, I felt if I could get actionable, helpful information regarding my health, I needed to get it. As a mom, I felt a parental responsibility to not bury my head in the sand, to meet with a certified genetic counselor.

When women take care of their health, they become their own best friend.

— Maya Angelou

About 3 weeks after meeting with a certified genetic counselor and having my blood drawn for genetic testing, I discovered I was positive for a BRCA1 gene mutation, too. The certified genetic counselor referred me to see a medical oncologist who specialized in high-risk patients. I was immediately compelled to share my genetic testing results in an e-mail to a few close friends and, of course, to my family, especially since many of them could be at risk, too. This is what I wrote: »

PATIENT PERSPECTIVE

DECEMBER 12, 2009

Family & Friends:

Unfortunately, I tested positive for the BRCA1 gene mutation #5385 (also known as #5382), the same gene mutation as Jan. It's 1 of the 3 BRCA mutations associated with people of Ashkenazi Jewish descent. It's most definitely what dad's mom Lillian had and eventually died from...

Jon and I will meet with a medical oncologist who specializes in genetic patients at high risk for breast and ovarian cancer in the next few weeks. I may have some major decisions to make regarding my female reproductive organs.

—Amy



Top: Amy Byer Shainman's grandmother.
Bottom: Amy Byer Shainman with her sister, Jan.

There are 3 specific mutations deemed "founder mutations" that are more common in people of Ashkenazi Jewish descent. Approximately 1 in 43 Ashkenazi Jews carry a BRCA mutation.

— Ellen Matloff, MS, CGC, CEO, My Gene Counsel

Jon and I didn't thoroughly understand exactly what having this genetic mutation meant for me, but we did realize that this information was about to lead my life, our marriage, and our family down a different path. As I actively began researching BRCA, neurosis kicked in and I found myself constantly thinking about my breasts. A few times every day I would feel my breasts, checking them for lumps. All the visuals in my life suddenly became about my breasts: making breakfast, 2 eggs sunny side up; driving in my car I'd see a bicyclist, the 2 wheels on the bicycle riding down the street; change for a dollar at the store, 2 quarters. Any image with 2 circles and breasts was all I could see.

The future of a woman carrying a BRCA mutation (or any other hereditary cancer syndrome) is fundamentally changed by that knowledge—and yet it remains just as fundamentally uncertain. For some women, the genetic diagnosis is all consuming. It is as if their lives and energies are spent anticipating cancer and imagining survivorship—from an illness they have not yet developed. A disturbing new word, with a distinctly Orwellian ring, has been coined to describe these women: "previvors"—pre-survivors...the prophylactic treatments...mastectomy, hormonal therapy—all entail physical and psychological anguish and carry risks in their own right.

— Siddhartha Mukherjee, MD, DPhil, in his book, *The Gene*

My annual checkup would now include a transvaginal ultrasound, even though transvaginal ultrasounds aren't 100% effective at detecting ovarian cancer. In addition, I would alternate every 6 months having a mammogram with a breast ultrasound and breast magnetic resonance imaging. I was aware it was important to get these tests done, but nonetheless, I had major anxiety. Knowing my genetic status was so all-consuming that I wished I could just "check out" for several weeks while processing all the information and hook myself up to a Prozac drip. However, I was a mom and there was the matter of taking care of the kids, so checking out for me was not an option.

My medical oncologist, Elisabeth McKeen, MD, FACP, gave me a rundown on my situation:

1. To reduce breast cancer risk:

- Enhanced surveillance/monitoring
- Medication: tamoxifen (lacks sufficient research on whether it is good for hereditary cancers)
- Prophylactic surgery. Removing breasts reduces a person's cancer risk by 95%, and my doctor believes it's more likely 98% when

you have a surgeon who is aggressive in removing breast tissue. Plus, it's better to place breast implants behind the muscle, so any future issue (cancer) is much easier to feel/detect.

2. To reduce ovarian cancer risk:

- Enhanced surveillance is, unfortunately, not effective at this juncture, and it is highly recommended that BRCA1 carriers have their ovaries removed between ages 35 to 40 or after childbearing is complete. My situation warranted a full hysterectomy as my sister Jan also had uterine cancer, which meant that I now had a "family history" of uterine cancer in a first-degree relative. Removing ovaries before natural menopause also reduces your breast cancer risk by 50%.
- There may be some benefit with the use of birth control pills.

3. Melanoma. McKeen sees many BRCA patients with melanoma and recommends an annual dermatological exam and formal eye exam, as melanoma can also manifest in the eye.

4. A colonoscopy at 50 years.

5. BRCA1 in men. My doctor admits that doctors may not be well versed or have any knowledge about BRCA1. She has seen men with the BRCA1 gene mutation develop prostate cancer and advises BRCA1-positive men to start full prostate exams by age 40.

6. Psychologist. The protocol demands that I need to see a psychologist, as there are ramifications to undergoing these prophylactic surgeries. My daughter also needs to consider certified genetic counseling and genetic testing by age 25. At 25, BRCA-positive women need to consider starting enhanced breast screenings. My son needs to consider genetic counseling and genetic testing by age 40 as that is when he would need to start full prostate exams.

The therapist I was required to see before surgery said one thing, which stuck with me: "Make sure you are at peace with your decision—whatever that is. Once it is done, it is done. Once they roll you into surgery, there is no going back. You have to make sure you are at peace with whatever you decide."

I was told my individual lifetime risk for ovarian cancer was as high as 50%. For me, I could not gamble with the silent thunder of that disease, especially since there are still no accurate surveillance methods to detect it. I knew deep inside that my sister was lucky. I couldn't play Russian roulette with my life. I had to do what was in my best interest—remaining breathing.

In the pre-op area awaiting my oophorectomy and hysterectomy, the gravity of what I was about to do hit me hard. I was not going to be able to have any more children. The thought of jumping up out of the bed and running out of the hospital more than crossed my mind. However, something was holding me down. Both a physical and emotional weight, an arm on my thigh, was not letting me get up, and a voice was keeping me there saying I needed to do this now, it was not a good idea for me to wait. Although she died at age 33 in 1934, my grandmother Lillian's presence was right there in the room. Her message to me was loud and clear:

This is what you need to do to be here, Amy. You need to do this to live. Do what I couldn't...and go save your life. ♦

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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 $\geq 20\%$) 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 $\geq 20\%$) 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 $\geq 20\%$) 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 $\geq 20\%$) 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.

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 serum¹ [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.

DARZALEX® (daratumumab) injection

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

Adverse Reaction	DARZALEX 16 mg/kg N=156 Incidence (%)		
	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 binding¹ [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.

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.

REFERENCES

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, *Transfusion*, 55:1545-1554 (accessible at <http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf>).

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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Transitions in Cancer Care—Moving From Crisis Intervention to Care Planning and Management

Rufus Collea, MD; Linda Pulver, RN, BA; Claire Ralli, LCSW; and Amanda Burgess, RN, OCN



COLLEA



PULVER

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ALTHOUGH THE US HEALTHCARE LANDSCAPE appears to be shifting yet again with a new Congress and administration vowing to replace the Affordable Care Act 7 years after its passage, at least one trend remains stable: the healthcare sector will continue to shift towards becoming more patient-centered, while emphasizing quality and improved, measurable outcomes of the population served.

Further, the rise of new value-based payment models that prioritize quality over quantity of services will lead to new benchmarks for care. This, in turn, is driving the redesign of our healthcare delivery model, transforming it into one that puts patients and families at the center of care management. Increasingly, providers are beginning to organize into integrated practice units (IPUs) and integrated care delivery systems that shift providers away from their traditional role as siloed institutions and towards a more cohesive network of care delivery.¹

These trends are both good for the patient and good for the payer, as providers who are implementing new models are seeing and experiencing on the front lines of care.

Nowhere could this trend be more evident than in the oncology sector, where a major reorganization in the way cancer treatment is delivered is currently underway. Patients and families have become essential voices in decisions on care delivery and the care experience. Embracing this new model of team-based care, in which responsibility for a patient's well-being is shared among clinical and nonclinical staff alike, will lead to more integrated, interdisciplinary units while improving quality and lowering costs across the spectrum.

As we fully embrace this new model of oncology care delivery, it is crucial that communication and information sharing among care providers continue to develop, while workflows between different segments of the care cycle remain integrated. Three key areas lie at the forefront of this shift:

- Prescription and delivery of palliative care
- An increasingly important role for clinical staff in navigating a patient through the treatment process
- The ever-increasing importance of interdisciplinary patient-centered communication through the Family Meeting Model

EMBRACING THIS NEW MODEL OF TEAM-BASED CARE WILL LEAD TO MORE INTEGRATED, INTERDISCIPLINARY UNITS WHILE IMPROVING QUALITY AND LOWERING COSTS ACROSS THE SPECTRUM.

Modernizing Palliative Care Delivery

The transition to a patient-centered care model must include thorough attention to the enormous role palliative care plays in cancer treatment. Palliative care is a critical component of cancer treatment due to its focus on improving both a patient's functional status and overall quality of life, regardless of treatment outcomes. Recently,

palliative care has gained attention as a specialty that is critical to improving patient quality of life while also improving efficiencies.

This is good news for the transition to patient-centered care, as palliative care, especially specialized palliative care, has been proven to reduce hospital stay lengths, lower provider expenditures, and free up resources previously devoted to critical care. On average, palliative care consultations result in savings of up to \$1.3 million for a 300-bed community hospital and up to \$2.5 million for the average academic medical center.² Palliative care also plays a role in improving patient survival rates, since the relief from pain and symptoms of cancer treatment actually helps patients complete their course of treatment.³ Furthermore, palliative care intervention can be a crucial window into exploring the value of treatment, enabling patients and families to make better decisions regarding their goals for care.

For this to happen, however, substantial changes must be made in the realm of palliative care delivery:

- Patients should be afforded increased access to specialist services so that high-quality palliative care can be available to more people.
- Palliative care delivery must move beyond inpatient and outpatient consultations. Patients, providers, and practitioners must be committed to moving palliative care forward to reach individuals earlier in their course of illness. This can be done by exploring open-access models that allow palliative and cancer treatments to be pursued simultaneously, as is currently allowed by CMS' Care Choices Model.⁴
- Stronger patient outreach and education initiatives and improved physician-patient communication is critical to ensuring that patients and doctors are aware of all available options. Efforts must be undertaken to ensure practitioners are well-versed in primary palliative care so that some of the basic elements of palliative care can be delivered early in a patient's treatment regimen.⁵
- Practitioners will need innovative approaches to delivering services to all patients, especially the seriously or terminally ill.

Such a cultural change in palliative care delivery can encourage patients and their families to become more engaged with practitioners, opening the door for better physician-patient relationships and easing the transition to a better patient-centered model of cancer care delivery.

Early Success in New Care Models

New York Oncology Hematology (NYOH), a leading provider of community-based cancer care services, has started implementing many of these approaches to palliative care delivery, with positive, measurable results. At a time when services are generally restricted to the inpatient and home settings, NYOH's team has experimented with bringing services into the outpatient community setting, expanding access for patients while maintaining a high quality of care.

CARE COLLABORATION



Versatile interdisciplinary teams are key to ensure patient-centered care.

NYOH's palliative care program is helping change the perception of palliative care: applying this integrated, coordinated approach to a mainstream care model that is available to all oncology patients has moved the perception away from that of a "crisis intervention" service that is typically assigned only to patients in a serious condition or near end-of-life.

Improving Navigation and Social Work Services

Physician practices are just 1 component of the oncology clinical setting. Equally important are the roles played by nonclinical interdisciplinary teams whose holistic management services impact a patient's care plan, care experience, and overall well-being. Such an interdisciplinary team—which includes nonclinical staff, social workers, and nurse navigators—provides a critical link between the patient and the rest of the healthcare delivery process. This "navigation team" provides continuity of care over the course of treatment and ensures that important details are addressed as a patient transitions throughout the healthcare continuum. One way to enhance this coordination, and develop effective navigation teams, is to look at the strategies undertaken by IPU and integrated care delivery systems. These networks have been successful in ensuring patients are cared for throughout the duration of their treatment, thanks to robust and effective interdisciplinary teams.¹

Any transition towards a patient-centered care model should ensure that special attention is paid to social workers, whose role in a patient's treatment and recovery extends far beyond what a physician alone can provide. Social workers meet patients and families where they are at any given moment: at home, at the hospital, or in a community care setting. They are trained to deal with the psychological issues associated with chronic illness that many medical providers may not be equipped to observe or address. By listening to the patient and their family, social workers focus on bringing to light the mind, body, and spirit connection element of an illness, and they work on integrating it into the patient's care plan. Any movement towards patient-centered care would benefit by ensuring that the interdisciplinary team remains an integral part of the care delivery model.

Improved Physician-Family Communication and the Family Meeting Model

The transition to patient-centered oncology care would be incomplete without open physician-patient communication and the full involvement of a patient's family. Therefore, it is necessary

to develop family support structures to facilitate communication among physicians, patients, and families.

Recent studies reveal significant room for improvement in the area of the physician-patient communication. Studies have found a high degree of discordance between the prognoses held by a physician and that physician's oncology patient. Patients are often more optimistic about their prognoses than their doctors, and they are usually unaware that discrepancies exist between the two. A study of 236 oncology patients found that 68% of patient-oncologist survival prognosis ratings were discordant. About 89% of discordant patients did not know that their opinions differed from those of their oncologists. Nearly all believed that their prognoses were better than their doctors' professional opinions.⁶

Meanwhile, oncologists and other specialists also face significant challenges with delivering bad news. Researchers in the conversation analysis field have consistently demonstrated that even when physicians are experienced in delivering bad prognoses, there is still an incentive to downplay or avoid giving the bad news. A study by Elizabeth Lamont and Nicholas Christakis found that physicians provided completely honest answers to patients only 37% of the time regarding their survival estimates, even when patients explicitly requested the information.⁷ Instead, doctors preferred to give inaccurate information (40% of the time, according to the study) or none at all (22.7% of the time). This trend held true even for patients with advanced or incurable cancer diagnoses. Clearly, there is a need for a better model of direct and honest physician-patient communication.

Fortunately, programs that emphasize patient-centered communication and family involvement have been shown to have a substantial impact on a patient's well-being. The Values and Options in Cancer Care study, conducted by researchers at cancer clinics in western New York and northern California, found that individualized communication training programs for oncologists can result in clinically and statistically significant improvements in physician-patient communication.⁸ Participants who received the training scored better on the researchers' composite measures of physician-patient communication than those who didn't receive the training.

Furthermore, the Family Meeting model, which recognizes that cancer »



RALLI



BURGESS

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ON AVERAGE, PALLIATIVE CARE CONSULTATIONS RESULT IN SAVINGS OF UP TO \$1.3 MILLION FOR A 300-BED COMMUNITY HOSPITAL AND UP TO \$2.5 MILLION FOR THE AVERAGE ACADEMIC MEDICAL CENTER.

CARE COLLABORATION

care frequently involves the patient's entire family, can be an effective approach to developing sound patient-centered care. By recognizing that patients are almost never alone in facing their cancer treatment, practitioners—oncologists, nurses, and social workers alike—can orient their practice to be more patient-focused.

Paolo Gritti at the Second University of Naples has outlined several methods for implementing the Family Meeting model.⁹ It begins with the need to create a setting where open, frank discussions on patient health can take place. Oncology practitioners implementing the Family Meeting model should then be prepared to do the following:

- Share complete and accurate information about the patient's diagnosis, condition, and prognosis.
- Discuss quality of care and establish an understanding of the patient's/family's views on cancer treatment and their goals for care.
- Inquire about how the family is coping or planning to cope with the disease and develop coping strategies.
- Recognize individuals' emotions surrounding the patient's diagnosis and account for differing feelings among family members.

At NYOH, practitioners are moving towards their own Family Meeting model to move cancer care from a reactive to a proactive process. Team members are coming together to share and develop a care plan that is driven by patient and family needs and goals, which reflects the whole patient experience. This is done via a forum where families can be educated and can discuss care options prior to an actual crisis. The NYOH Family Meeting model also encourages patients to be empowered to identify personal goals related to their treatment in a setting that welcomes open and honest discussion of all aspects of health, including topics previously considered taboo.

Conclusion

The transition to value-based, patient-centered care is not always simple or straightforward. However, with versatile interdisciplinary teams using effective tools and strategies that recognize the value of the patient and their support system in the treatment process, community-based cancer providers are measurably improving the care experience and outcomes for their patients. ♦

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CONFERENCE COVERAGE: NATIONAL COMPREHENSIVE CANCER NETWORK

Helping Cancer Patients Quit Smoking Through Counseling and Pharmacotherapy

Christina Mattina



CINCIRIPINI

AT THE 22ND ANNUAL CONFERENCE of the National Comprehensive Cancer Network (NCCN), in Orlando, Florida, Paul M. Cinciripini, PhD, of The University of Texas MD Anderson Cancer Center, delivered a presentation on a mission he said he has spent the better part of his life working on: getting patients with cancer to quit smoking cigarettes.

Cinciripini, who serves as professor and chair for the Department of Behavioral Science as well as director of the Tobacco Treatment Program at MD Anderson, acknowledged that the audience of mainly oncologists did not need to be convinced that smoking is harmful. He discussed data which indicate over 480,000 deaths per year in the United States are attributable to cigarette smoking, and summarized the beneficial effects of cessation, including reduced depression, anxiety, and stress, along with improved positive mood and quality of life (QOL).

These outcomes, both the dangers of smoking and the benefits of cessation, are magnified in cancer patients, Cinciripini explained. Smoking during cancer treatment is associated with an increased risk of recurrence, greater symptom burden, and reduced survival. Response to radiotherapy is diminished in smokers, and they have an increased risk of pulmonary embolism, infection, and poor wound healing. Smokers also experience worsened toxicities and immune impairment while undergoing chemotherapy, and the efficacy of the treatment is diminished.

In one study, patients who quit smoking had a 78% overall survival rate 2 years after radiotherapy compared with 69% among those who continued to smoke. From a QOL perspective, cancer patients who quit smoking report easier breathing and a boost in energy. Clearly, Cinciripini said, there is a need for intervention among this population.

The most effective interventions, he explained, involve a combination of counseling and medications. Recommended first-line medications include varenicline, bupropion, and nicotine-replacement therapies like patches or gum. Cinciripini cited the EAGLES trial that found varenicline to be more effective than bupropion, nicotine patch, or placebo in patients with and without psychiatric disorders. The occurrence of severe neuropsychiatric events during treatment, including suicide, was similar across all tested therapies. Cinciripini nonetheless advised clinicians to think about the patient's psychiatric background and history when prescribing these treatments, and to "be on the lookout for any untoward changes in their psychiatric profile."

He then highlighted several studies demonstrating better cessation rates associated with higher intensity counseling, defined as more than 4 sessions lasting 30 to 300 minutes, compared with minimal intensity counseling. Although this more intense treatment costs more, Cinciripini explained that its increased effectiveness makes it more cost-effective. He also cited research that found a combination of intense counseling plus the introduction of nicotine replacement therapy before quitting was more effective at 16 and 26 weeks than either intervention alone.

After presenting this literature, Cinciripini discussed the NCCN clinical guidelines for smoking cessation in oncology. First, clinicians must assess patients' nicotine dependency, history of quit attempts, and readiness to quit. If a patient is ready to quit, the clinician should involve him or her in establishing a plan and setting a quit date. If he or she is not ready, the clinician can help address concerns and suggest pharmacotherapy to reduce the number of cigarettes smoked per day. The goal of this reduction is eventually quitting, Cinciripini emphasized, not just harm reduction.

The primary recommended therapies are a combination of behavioral therapy and either nicotine replacement therapies or varenicline. If a patient

succeeds in quitting, the guidelines recommend "motivational strategies for continued abstinence." If a patient relapses, clinicians can switch the type of therapy, but must be sure to maintain consistent engagement with the patient.

Smoking cessation is "not a one and done" event, Cinciripini emphasized, and requires consistent contact and follow-up by the clinician. "If they quit, great, stay engaged. If they don't, great, stay engaged," he summarized. When the audience was invited to ask questions, an attendee asked Cinciripini his opinion on e-cigarettes as a form of risk mitigation, although he'd previously said he was focusing on complete cessation, not harm reduction.

"I knew I was going to get that question," Cinciripini sighed jokingly. "The answer is, it depends."

While there isn't enough data to establish effectiveness and long-term safety for the devices, he said, the reduction in carcinogens makes it preferable to cigarettes and can provide an opening for patients to transition toward eliminating nicotine. Cinciripini said he would not rule out e-cigarettes as a potential tool if researchers had more data, but reiterated he was "most comfortable talking about valid nicotine therapies" as a means for cessation. ♦

Radiation Therapy Updates for Breast Cancer in the NCCN Guidelines

Surabhi Dangi-Garimella, PhD



SALERNO

ON THE SECOND DAY OF THE 22nd Annual Conference of the National Comprehensive Cancer Network (NCCN), in Orlando, Florida, Kilian E. Salerno, MD, of the Roswell Park Cancer Institute, walked the audience through updates to the NCCN Guidelines, explaining clinical situations in which radiation is indicated, appropriate targets of radiation treatment, and optimal approaches for minimizing toxicity.

Understanding the target area is important, Salerno said, because the treatment options and the treatment plan and delivery need to be optimized per the patient's needs. "The target region to receive the radiation dose can vary. It might be the whole breast; partial breast, where we may target the lumpectomy cavity; the chest wall; or just regional nodes."

The dose varies according to the target region:

1. Conventional fractionation is a dose of 1.8 to 2 Gy per fraction, for a total dose of 45 to 50.4 Gy.
2. Hypofractionation is typically a shorter course that uses larger doses per fraction. More than 2 Gy may be used per fraction to lower the total dose, which can be:
 - 40.05 to 42.56 Gy given in daily fractions for whole breast radiation
 - 34-38.5 Gy administered as twice daily fractions for partial breast radiation
3. The accelerated course is usually treatment over a shorter time course. Clinics have several options for the source of radiation to choose from, Salerno said. The sources of radiation include:
 - External beam (photons, electrons, proton beam)
 - Brachytherapy (radioactive source or catheters)
 - Intraoperative devices

The NCCN Guidelines for breast cancer, updated in March 2017,¹ provide guidance on target definition and optimizing therapy for an individual patient as needed. "Greater target dose homogeneity and sparing of normal tissues can be accomplished using compensators such as wedges, forward planning using segments, and intensity-modulated radiation therapy," the guidelines stated. »

The most commonly used techniques include:

- Positioning: supine versus prone. Salerno said that the prone position is used to identify hot spots and minimize damage to normal tissue. It is most typically used for early-stage disease when the whole breast is the target, and it ensures the normal tissue is not affected.
- Computed tomography for based planning
- Three dimensionally planned conformal radiotherapy versus immune-modulated radiation therapy
- Respiratory gating, where the patient controls respiration. This technique requires extra time, personnel, planning, and time for treatment, Salerno said.

The updated guidelines also provide information on patients who have undergone breast conservation but in whom radiation therapy is contraindicated. An absolute “No” includes:

- Pregnancy
- Diffuse suspicious or malignant-appearing microcalcifications
- Diffusely positive pathologic margins
- Homozygous for *ATM* mutations

“IDENTIFYING AN APPROPRIATE MARGIN HAS BEEN A TOPIC OF DEBATE AND THE NEW GUIDELINE PROVIDES DIRECTION.”

—Kilian E. Salerno, MD

remember, though, that context matters.” The following 2 recommendations have been added to the Guideline:

- 2 mm is considered an adequate margin² in ductal carcinoma in situ treated with whole-breast irradiation.
- For stage I-II invasive disease treated with whole-breast irradiation, no tumor on ink is considered an adequate margin.

Salerno then spoke about locoregional treatment of clinical stage I, IIA, or IIIB disease or node-positive disease. For negative axillary nodes, the following treatment options have been recommended:

- Radiation therapy to the whole breast, with or without boost to the tumor bed; preferably hypofractionation
- Accelerated partial breast irradiation in some low-risk patients, following guidelines defined by the American Society of Radiation Oncology, which, Salerno said, will be updated in the coming year.

She then provided insight on post-mastectomy radiation (PMRT), classic indications for which include 4 or more positive axillary lymph nodes, positive margins, and tumor size over 5 cm. However, patients with 1 to 3 lymph nodes, close margins and some high-risk features, such as age, extracapsular extension, and certain intrinsic subtypes, could also be considered for PMRT.

Regional node irradiation or RNI is recommended for those with 4 or more positive nodes, strongly considered for 1 to 3 positive nodes, and may be considered for some high-risk node negative patients. ♦

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Personalized Care in Lung Cancer Is All About the Molecular Subtype

Surabhi Dangi-Garimella, PhD



RIELY

AT THE 22ND ANNUAL CONFERENCE of the National Comprehensive Cancer Network (NCCN), held in Orlando, Florida, Gregory J. Riely, MD, PhD, Memorial Sloan Kettering Cancer Center, spoke about the what, when, and how of biomarker testing in non-small cell lung cancer.

Biomarker testing is essential in lung cancer, Riely said, and should be done at diagnosis. “Even if it is not done at diagnosis, testing before the choice of second-line therapy is valuable as well.”

Riely showed the scanned image of the lungs of a woman who presented with an adenocarcinoma. Diagnosis of an adenocarcinoma may not be as bad as it was a decade ago, he said, adding, “We need to identify biomarkers for this, which, today, can start with molecular analysis and PD-L1 testing.”

Based on the results of the molecular analysis, the patient may receive:

- Targeted therapy if positive for *EGFR*, *ALK*, or *ROS1* mutations
- Platinum-based chemotherapy if PD-L1 expression is <50%
- Pembrolizumab if PD-L1 expression is >50%

“Current NCCN Guidelines for a patient who presents with metastatic disease recommend molecular testing to establish histologic subtype, smoking cessation counseling, and palliative care. For all the various histological subtypes, molecular testing is central,” Riely said. The key thing is to conduct these tests as part of a broad molecular testing profile. An important consideration is multiplexing to be able to maximize on the small biopsy sample.

Molecular testing for lung cancer has focused on DNA-based tests like sequencing and fluorescence in situ hybridization, known as FISH. But over the past few years, protein tests have grown in usage, primarily immunohistochemistry.

Riely then shared phase 3 results from the KEYNOTE-024 trial that were presented at the annual meeting of the European Society for Medical Oncology last year and published in the *New England Journal of Medicine*, which showed that pembrolizumab was effective in advanced lung cancer, compared with platinum-based chemotherapy, when PD-L1 was expressed in at least 50% of tumor cells.¹

“However, PD-L1 tests are all over the map, so how do you choose?” asked Riely. The fact that each PD-1 inhibitor introduced and approved has developed a complementary assay to test PD-L1 expression in the tumor samples makes it challenging to figure out how all these tests compare.

A recently published study in *JAMA Oncology* compared 4 such PD-L1 assays, and found that while the tests were analytically interchangeable, they had not been cross-validated. Further, only 3 of the 4 assays were concordant and reproducible.²

An important point that Riely noted during his presentation was that PD-L1 expression is probably stable and there is no clear benefit to repeat a biopsy unless the prior sample is exhausted.

It’s also important, to customize biomarker testing needs based on the institution.

“Often, institutions use a combination of tactics to achieve comprehensive evaluation in a timely manner,” Riely said. ♦

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CONFERENCE COVERAGE: NATIONAL COMPREHENSIVE CANCER NETWORK

Multigene Panels Important for Precision Cancer Care; Variance and Coverage Barriers Remain

Surabhi Dangi-Garimella, PhD



OFFIT

WHILE WE HAVE LONG FORGOTTEN the Mendelian models and single-gene testing panels in the field of oncology, we have not yet reached agnostic testing or population screening for cancer—although we are headed in that direction, according to Kenneth Offit, MD, MPH, from Memorial Sloan Kettering Cancer Center (MSKCC).

Speaking at the 22nd Annual Conference of the National Comprehensive Cancer Network held in Orlando, Florida, Offit explained that hereditary factors are responsible for 16% of cancers, behind smoking (33%) and obesity (20%).

Paying attention to these known risk factors of cancer can reduce the possibility of cancer-related deaths by 60%.

The Utah genealogical experiment led to the discovery of the *BRCA* gene and its importance in familial cancers, Offit explained, and paved the way for the role of *BRCA* in cancer development among Ashkenazi Jewish women.¹ While a single *BRCA1* mutation has been noted in 20% of Ashkenazi Jewish women with early onset breast cancer; add to that a frameshift mutation in *BRCA2* could lead to 25% of all early-onset breast cancer cases in Ashkenazi Jewish women who have a personal or family history of ovarian cancer.

Knowledge of personal and inherited predisposition to mutations can help oncologists devise a more informed approach to treatment decisions.

A more recent study, published in *JAMA Oncology*, followed *BRCA1*-positive women and found they have an increased risk of serous or serous-like endometrial cancer.² These findings bring into perspective the need to discuss the advantages of preventive hysterectomy in these women, Offit explained. In the case of familial adenomatous polyposis, where a 100% penetrance of adenomas is seen, and there is a high risk of extracolonic tumors.

“If left untreated, these polyps can lead to cancer,” said Offit. “Testing for a mutation in *APC* becomes important, and a prophylactic colectomy may be needed in teen years.” He then provided a list of the various tumor sites and the known mutations associated with that form of cancer:

- Gastrointestinal stromal tumor (*KIT*)
- Thyroid (*RET*)
- Stomach (*CDH1*)
- Kidney (*STK11*, *VHL*, *BHD*, *TS*)
- Basal cell (*PTCH*)
- Colon (*MLH1*, *MSH2*)
- Colon (*APC*)
- Breast/ovary (*BRCA1/2*, *PALB2*, *CHEK2*)

He explained that while multiple genes may be mutated with a specific cancer type, the risks vary.

“For example, in breast cancer, mutations in *BRCA1/2* have a significant bearing on the risk on developing the cancer, while mutation in *ATM* have a lower risk.” Despite this knowledge, the “Forces of change have led to commercialization of multigene testing,” he said.

Offit explained that scientists like himself were concerned with the rate at which these tests were being developed and introduced in the market. They raised their voices through editorials and at meetings, warning against inadequate knowledge to use these panels in decision making.

About 20% to 30% of multigene panels yield variants of uncertain significance, which may not necessarily affect protein function or be clinically relevant, Offit said. This might be because not many sequencing studies have been conducted, he added.

The Prospective Registry of MultiPlex Testing or PROMPT registry,² developed by MSKCC in collaboration with other academic research institutions and labo-

ratories, allows patients to input information from their multiplex genetic testing and have a mutation in any gene other than *BRCA1/2*.

“This will provide healthcare providers and researchers better access to uncommon or rare gene variants,” Offit said.

But will payers provide coverage for these tests?

A study recently published in the *Journal of the National Comprehensive Cancer Network*, which conducted semi-structured interviews with 11 major US payers, found that main barriers to coverage for hereditary cancer panels included poor fit with coverage frameworks, insufficient evidence, departure from pedigree-based testing for genetic screening, and lack of clinical testing rigor.⁴

Offit concluded his talk by stating that next generation sequencing has made multigene panel testing possible. “While the time for agnostic testing may be approaching, it’s not here yet, mainly because of variance and lack of payer coverage.” ♦

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Addressing the Roots of Disparities in Cancer Care: Inherent Bias, Resources, and Insurance

Surabhi Dangi-Garimella, PhD



GOODMAN



ALLEN

AT THE 22ND ANNUAL Conference of the National Comprehensive Cancer Network: Improving the Quality, Effectiveness, and Efficiency of Cancer Care, held March 23-25, 2017, in Orlando, Florida, policy researchers with interest in cancer care disparities discussed the source of existing disparities and how they can be successfully addressed.

Cliff Goodman, PhD, senior vice president, The Lewin Group, led the panelists—Shauntice Allen, PhD, University of Alabama at Birmingham Comprehensive Cancer Center; Moon S. Chen, Jr, PhD, MPH, associate director for cancer control, University of California Davis Comprehensive Cancer Center; Anne Filipic, Enroll America; Edith Mitchell, MD, Sidney Kimmel Cancer Center at Jefferson; and Phyllis Pettit Nassi, MSW, Huntsman Cancer Institute at the University of Utah—through a very interesting discussion that touched on racial, gender, genomic, perspective, economic, and geographic bias.

“Disparities, even if they are not made worse by the replacement healthcare law, are at risk of getting worse,” Goodman said, addressing the panel. “What do these disparities look like? Has [the Affordable Care Act] done anything to reduce them? Financial toxicity: is it harder for certain populations? Can providers introduce bias?”

Allen, who has been diagnosed with cancer herself, said that her motivation to work in the field of cancer disparities is to show that cancer is not a death sentence. “We need to be open to having the conversation and till we are open to doing that, disparities will continue. I think there are differences in how »

CONFERENCE COVERAGE: NATIONAL COMPREHENSIVE CANCER NETWORK



CHEN

individuals are treated and how the discussions are introduced to people,” she said.

Filipic believes that developing outreach strategies for Americans and figuring out ways to talk about the advantages of enrolling on a healthcare plan to the common man is a viable strategy.

“It is important to ensure that physicians and researchers understand how difficult it is to make it right and how bad it would be if they get it wrong,” Nassi said. “American Indians are dealing with a different health system: the Indian Health Service. This brings geography into play. We have to consider here the fact that this is a medical service that is underfunded—for every dollar they request, they get 13 cents to 24 cents.”



FILIPIC

Mitchell explained that African American women have triple the levels of triple-negative breast cancer, so although the incidence is not high, death rate due to the genomic nature of their disease augments the death rate. “Understanding disparities in America, working with the population and understanding the genomics that defines the population, is what I do,” she explained.



MITCHELL

Another example that Mitchell provided was of colon cancer, which has a 20% higher incidence in African Americans and a 40% higher death rate. Further, incidence is much earlier in this population. “So understanding these individuals, understanding their disease profile and treating them accordingly is important,” she added.

Mitchell emphasized the importance of having an open conversation with patients on clinical trial participation. “Don’t assume, because that can introduce bias. Open a conversation and understand what the individuals want,” she said.



NASSI

Filipic said that the Affordable Care Act (ACA) tried to address these disparities. “Since the ACA was passed in 2010, over 22 million gained health coverage with the available provisions. The uninsured rate nearly halved from 2014 (about 16%) to 2016 (under 9%). Across all demographic groups, a reduction in the uninsured rate has been seen.”

“Congress will be voting on the AHCA [American Health Care Act] later today,” Filipic said. [Ed note: The new version of the AHCA passed the House and is now waiting for a vote in the Senate]. When questioned about her own leaning for the ACA, she said, “While I have bias, many cancer societies have expressed concerns about the AHCA. The Congressional Budget Office, which is a nonpartisan institution, has projected that 14 million would lose coverage by 2018.² Cost is king...whether it is Medicaid expansion or the tax credits that bring affordable coverage within reach. So ultimately, we are seeing that lower income and sicker individuals stand to lose in this proposal.”

“THOSE OF US WORKING WITHIN CANCER SYSTEMS, WE FORGET THAT PROVIDERS IN CLINICS OR IN THE COMMUNITY DO NOT HAVE THE SAME RESOURCES.”

—Phyllis Pettit Nassi, MSW

“Disparities are already hard to manage, and with 14 million losing coverage will have an interesting effect on the population,” said Allen.

Nassi emphasized the importance of reaching out to community clinics that often work under constrained resources. “Those of us working within cancer systems, we forget that providers in clinics

or in the community do not have the same resources. Doctors tell us ‘If we don’t treat it, we don’t look for it.’ So sometimes the bias is inherent because of financial situations.”

“One potential area of bias is who gets recruited in clinical trials. So, if a provider cannot speak the patient’s language, he may not spend the time to explain the advantages of participating in a trial or the assumption that the patient may not want to participate,” Chen said.

Tapping into her years of experience as an oncologist, Mitchell said the zip code is a good identifier of disparities. “So one of the things we need to do is give individualized medicine that is not based on where they live but what their medical status is,” she said.

Nassi explained that at Hunstman, “We are doing outreach, pushing screening, trying to educate. But the resources do not exist in the communities. Cancer centers, on the other hand, do have the resources...so we need to go to them with the resources.” She explained, however, that there need to be a plan in place after a person is diagnosed, because treating 1 individual with cancer in the American Indian community can wipe out the budget for the community.

Filipic explained that the perception of affordability is also a bias. She shared an example of a woman from a focus group conducted by Enroll America, who did not have any knowledge on the healthcare coverage options she had available on the ACA because she assumed she would not be able to afford the premium. “Many do not understand that there is affordable insurance and there are tax credits available,” she said.

“I have been a big proponent of the healthcare institution understanding the patient population—who they are and getting their community involved,” Mitchell explained. “For example, mammograms may not be covered by an individual’s insurance plan, but there may be community programs that provide free mammograms.” She added that her institution has made it more convenient for patients receiving cancer treatment to receive their care without having to forego their work hours or income, with extended chemotherapy care on weekends and walk-in clinics with more flexible hours.

“Cancer centers need to accept this challenge of addressing disparities. Once you make the commitment, and look beyond collecting data and getting the grant, we must go to the community and see what can be done there,” said Nassi. ♦

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2. Caffrey M. CBO projects 24 million would lose coverage by 2026 under Republican health plan. *The American Journal of Managed Care*® website. <http://www.ajmc.com/newsroom/cbo-projects-24-million-would-lose-coverage-by-2026-under-republican-health-plan>. Published March 13, 2017. Accessed March 23, 2017.



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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.

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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.



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 $\geq 38.5^{\circ}\text{C}$ 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 $>2.5 \times \text{ULN}$ 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 ($\geq 20\%$) 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 ($\geq 5\%$) 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.



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 $\geq 38.5^{\circ}\text{C}$ 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.

YONDELIS[®] (trabectedin) for injection

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 ($\geq 20\%$) were nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, and headache. The most common laboratory abnormalities ($\geq 20\%$) 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 $\geq 10\%$ 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 $\geq 10\%$ in the trabectedin arm and at a rate higher in the trabectedin arm compared with dacarbazine arm by $\geq 5\%$ in overall incidence or by $\geq 2\%$ 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 $\geq 5\%$ (all Grades) or by $\geq 2\%$ (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*].

YONDELIS® (trabectedin) for injection

Effect of Cytochrome CYP3A Inducers: Coadministration of YONDELIS with rifampin, a strong CYP3A inducer, decreased systemic exposure of trabectedin by 31%. Avoid using strong CYP3A inducers (e.g., rifampin, phenobarbital, St. John's wort) in patients taking YONDELIS [see *Clinical Pharmacology (12.3) in Full Prescribing Information*].

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: Based on its mechanism of action, trabectedin can cause fetal harm when administered during pregnancy [see *Clinical Pharmacology (12.1) in Full Prescribing Information*]. There are no available data with the use of YONDELIS during pregnancy. Animal reproductive and developmental studies at relevant doses have not been conducted with trabectedin; however, placental transfer of trabectedin was demonstrated in pregnant rats. Advise pregnant woman of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population are unknown; however, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Lactation: Risk Summary: There are no data on the presence of trabectedin in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions from YONDELIS in breastfed infants, advise a nursing woman to discontinue nursing during treatment with YONDELIS.

Females and Males of Reproductive Potential: Contraception: Females: Advise female patients of reproductive potential to use effective contraception during and for 2 months after the last dose of YONDELIS [see *Use in Specific Populations*]. **Males:** YONDELIS may damage spermatozoa, resulting in possible genetic and fetal abnormalities. Advise males with a female sexual partner of reproductive potential to use effective contraception during and for 5 months after the last dose of YONDELIS [see *Nonclinical Toxicology (13.1) in Full Prescribing Information*]. **Infertility:** YONDELIS may result in decreased fertility in males and females [see *Nonclinical Toxicology (13.1) in Full Prescribing Information*].

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Clinical studies of YONDELIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Hepatic Impairment: The mean trabectedin exposure was (97%) higher in patients with moderate (bilirubin levels 1.5 to 3.0 times the upper limit of normal, and AST and ALT less than 8 times the upper limit of normal) hepatic impairment compared to patients with normal (total bilirubin \leq the upper limit of normal, and AST and ALT \leq the upper limit of normal) liver function. Reduce YONDELIS dose in patients with moderate hepatic impairment [see *Dosage and Administration (2.1) and Clinical Pharmacology (12.3) in Full Prescribing Information*].

Do not administer YONDELIS to patients with severe hepatic impairment (bilirubin levels above 3 times to 10 times the upper limit of normal, and any AST and ALT) [see *Warnings and Precautions*].

Renal Impairment: No dose adjustment is recommended in patients with mild [creatinine clearance (CLcr) 60-89 mL/min] or moderate (CLcr of 30-59 mL/min) renal impairment.

The pharmacokinetics of trabectedin has not been evaluated in patients with severe renal impairment (CLcr $<$ 30 mL/min) or end stage renal disease [see *Clinical Pharmacology (12.3) in Full Prescribing Information*].

OVERDOSAGE

There is no specific antidote for YONDELIS. Hemodialysis is not expected to enhance the elimination of YONDELIS because trabectedin is highly bound to plasma proteins (97%) and not significantly renally excreted.

PATIENT COUNSELING INFORMATION

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

Myelosuppression: Inform patients of the risks of myelosuppression. Instruct patients to immediately contact their healthcare provider for fever or unusual bruising, bleeding, tiredness, or paleness.

Rhabdomyolysis: Advise patients to contact their healthcare provider if they experience severe muscle pain or weakness.

Hepatotoxicity: Advise patients to contact their healthcare provider immediately for yellowing of skin and eyes (jaundice), pain in the upper right quadrant, severe nausea or vomiting, difficulty in concentrating, disorientation, or confusion.

Cardiomyopathy: Advise patients to contact their healthcare provider for new onset chest pain, shortness of breath, fatigue, lower extremity edema, or heart palpitations.

Hypersensitivity: Advise patients to seek immediate medical attention for symptoms of allergic reactions including difficulty breathing, chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips or skin rash.

Extravasation: Inform patients of the risks of extravasation and to notify their healthcare provider for redness, swelling, itchiness and discomfort or leakage at the injection site.

Embryofetal toxicity: Advise pregnant women of the potential risk to a fetus. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with YONDELIS [see *Warnings and Precautions and Use in Specific Populations*].

Females and males of reproductive potential: Advise females of reproductive potential to use effective contraception during treatment with YONDELIS and for at least 2 months after last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with YONDELIS and for at least 5 months after the last dose [see *Warnings and Precautions and Use in Specific Populations*].

Lactation: Advise females not to breastfeed during treatment with YONDELIS [see *Use in Specific Populations*].

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Oncologists Believe Achieving Cancer Moonshot Goals Should Start in the Community

Surabhi Dangi-Garimella, PhD



HARWIN

FORMER VICE PRESIDENT JOE BIDEN'S Cancer Moonshot initiative¹ placed significant emphasis on the role of cancer centers in improving the nature of oncology care delivery in the country, ultimately to improve patient outcomes. However, community oncologists believe that they are in a very good position to lead the way.

Joining this discussion at the 2017 Community Oncology Conference, April 27-28, in National Harbor, Maryland, were William Harwin, MD, president and managing partner, Florida Cancer Specialists; Edward Licitra, MD, PhD, chief financial officer and director of revenue cycle, Central Jersey Division, Regional Cancer Care Associates (RCCA); and R. Steven Paulson, MD, President, Texas Oncology. Debra Patt, MD, MPH, MBA, vice president, Texas Oncology, moderated the discussion.



LICITRA

When asked about the role played by each of the practices in fueling Cancer Moonshot, Harwin said that many different factors can influence Cancer Moonshot, including developing a patient care system. “We have about 50 patient managers, many of whom work remotely,” he described. “We also have an active phase I unit on site, and that’s one of our biggest initiatives.”



PAULSON

As a result of requirements of the Oncology Care Model (OCM),² Harwin’s organization also has a care management team. “They are available 24 hours and provide triage, which is very valuable for our patients,” he said. The team members, Harwin added, adhere to protocols developed for triage management and psychosocial support.



PATT

Paulson noted, however, that the challenge with OCM is the upfront investment for additional staffing, to ensure that reporting requirements and change implementation can be met. Paulson also addressed the importance of extending clinic hours to avoid emergency room visits.

“OCM has given us the ability to focus and change culture,” Licitra emphasized. He explained that the changes that a practice infuses to meet OCM requirements are not restricted to Medicare patients; they extend to other patient populations as well. “While it is a work in progress, we are trying to centralize our processes,” he said, adding that RCCA is working with Innovative Oncology Business Solutions, co-founded by Barbara McAneny, MD, to bring this about.

“How important is research for your practice and how have you built it into your practice?” Patt asked the panelists. Licitra noted the importance of data integration to improve patient outcomes. RCCA is assembling all the genomics and proteomics information on patients and then trying to identify ways to improve outcomes. “We are using tools to understand both clinical and financial outcomes,” he added. “We need people to realize the value of community oncology and they come to us and give us the opportunity to care for them,” Licitra said.

Paulson explained that Texas Oncology has built relations with hospitals, clinics, and the pharmaceutical industry to help support their in-house research efforts. “We try to create a situation where the best molecules are accessible to our patients,” he said. He is, however, concerned with the low rate of clinical trial enrollment, especially among newly diagnosed patients.

Challenges to Delivering Research in the Community Setting

Patt indicated that in addition to operational costs, individual clinicians contributing time presents challenges. “What are the other challenges that you



Capital (ferris) Wheel at National Harbor, Maryland, USA.

face and how can they be overcome to facilitate research in the community clinic?” she asked.

Harwin said that his practice uses a clinical trial navigator, and it also employs Flatiron Health’s OncoAnalytics platform.³ “But we cannot replace physicians,” Harwin said, emphasizing the need to raise awareness through fellowship programs.

“Patient identification and physician engagement are key,” said Licitra, indicating that modifying physician compensation models can have a significant

impact. Paulson agreed with Licitra. “You can change reimbursement models to include financial incentives for participating in clinical trials,” he said, noting that community clinics should work towards the goal of providing patients access to a research platform.

Clinical trials enable huge savings because you don’t have to pay for the drugs, Harwin said. To ensure timeliness of acquiring information, “We have our own molecular testing

“WE CAN’T HAVE EVERY EXPERT AT EVERY SITE OF CARE, AND WE NEED TO IDENTIFY WAYS TO BRIDGE GEOGRAPHICAL GAPS.”

—Debra Patt, MD, MPH, MBA

facility,” Paulson said. It helps the clinic, too, to better aggregate the patient’s molecular data along with clinical information. “We have also created an outpatient interventional radiology facility, which costs half of what we would pay for if the patient goes to a hospital,” he added.

Patt noted the importance of clinical decision support, which allows quality improvement, faster treatment by helping with prior authorization, and better outcomes. She also emphasized the importance of telehealth for practices with multiple sites. “We can’t have every expert at every site of care, and we need to identify ways to bridge geographical gaps,” she explained, adding that telehealth services need to grow quickly “because we may not provide all services at every site across large practices.”

Licitra believes that curing cancer and curing the cancer care delivery systems are the targets of reimbursement models, and they are both significant challenges. However, Paulson said that even if doctors do not like these changes, it is important to climb on board since the OCM is fueling the opportunity to bring about changes.

Pratt noted the importance of community oncologists “telling their story.” “We need to allocate more time to this,” she said. ♦

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Linking Claims, Clinical Data Is Essential for a Learning Health System

Surabhi Dangi-Garimella, PhD



GREEN

“BIG DATA” IS A TERM USED AS COMMONLY as the term “value” in cancer care. However, similar to value, the interpretation of big data can vary, according to Robert Green, MD, vice president of clinical strategy and senior medical director at Flatiron Health. Is the rubber meeting the road with big data in cancer care? “No ... rather, not yet,” Green said at the 2017 Community Oncology Conference, held April 26-27 in National Harbor, Maryland.

Green explained that in order to make data from electronic health records useful, real-world quality data play an important role. However, it is also important to link clinical and claims data. “That’s where the future is,” he said.

Quoting quantitative scientist Gary King, PhD, from Harvard University, who said, “Big data is not about the data,” Green explained that it’s about using the data to generate meaningful insights. “At Flatiron, we define big data based on its complexity, rather than the volume.”

The focus should be on leveraging the data for high-value care, on improving outcomes, and accelerating clinical work, Green explained.

“We are being asked to develop interventions that will affect care and the financial viability of our practices,” he said. “To achieve this, we need to feed all this information back into our system to improve work flow...the concept of a learning system.”

He believes that processing structured data is key to be able to use these data, often described as “data scrubbing.” But a lot of information is not structured—such as pathology or physician notes—and a method needs to exist to extract this information.

“Unstructured data are typically hard to get at, and it’s not possible to get these data into a structured form, accurately, and use them to generate feedback and improve care,” he said.

Green told the audience, most of whom were oncology care providers, that although most providers think they are good at what they do for patients, “I don’t believe the metrics that I am reporting on are really bringing value to the patient because I checked the required box, such as measuring pain medication.” So, he asked, how do providers find out if they are taking good care of their patients?

“You don’t know how well your patients are doing unless you try to measure their performance,” Green said, and he outlined what is needed to generate real-world quality data:

Fill in the gaps. He stressed that filling in data gaps is very important to be able to mine high-quality data, and this means combining unstructured data with raw structured data.

Identify cohorts. Identify the appropriate patient cohort on which to conduct analyses. Defining the cohort is important when measuring quality to report on metrics.

Develop an analysis plan. Develop, document, and apply a rigorous plan. It is easy to miss the right answer if the data are not thoroughly evaluated, he said.

Case study 1. Green then provided a case study on assessing clinic adherence to *EGFR* and *ALK* testing in non-small-cell lung cancer (NSCLC). Analysis of Flatiron’s database found that only 21% of patients were tested across the network of practices that were conducting this genetic test.

“But when we drilled down even more, the median testing rate was 16%—some clinics were testing 100% while others were only testing infrequently,” he said.

So there was significant variance across clinics, which was apparent only when Flatiron analyzed the data at the individual clinic level.

Case study 2. Green showed that in their 2012-2014 data set, KRAS testing rates for colorectal cancer were 71% in 2012 and then just 57% in 2014. The variability was 90% to 35% across 21 clinics, and testing rates rose with later lines of therapy: 62% at first-line and 90% by third-line and above.

“Such detailed information can influence how we collect, analyze, and report on quality metrics and how it ultimately affects reimbursement in that practice,” Green said.

To highlight the importance of linking clinical and claims data, Green compared the value that claims data bring to quality analysis, and he also noted specific challenges. While claims data do provide insight into the total cost by disease type, and help identify cost drivers, drug compliance rates, and information on hospitalization and emergency department visits, that information is not sufficient, Green said. Claims data, he added, lack attribution and don’t have enough clinical depth to have a real influence on cost.

ACCORDING TO ROBERT GREEN, MD, CLAIMS DATA LACK ATTRIBUTION AND DON’T HAVE ENOUGH CLINICAL DEPTH TO HAVE A REAL INFLUENCE ON COST.

“There’s also data latency...claims data are not as recent as a clinic would like,” he added.

Circling back to how he kicked off his presentation, Green said “It’s not about the data, it’s about what you do with them.” He predicted that measurement and reporting of physician and clinical performance will soon become routine; personalized risk assessment will be essential for process improvements and to maximize returns; and outcomes improvement will become the expectation. ♦

Oncology Practice Administrators Discuss Early Findings From the OCM

Surabhi Dangi-Garimella, PhD



BAIRD



RAHMAN

ONCOLOGY PRACTICES THAT ARE participating in the Center for Medicare & Medicaid Innovation’s Oncology Care Model (OCM) have started receiving performance feedback from CMS. At the 2017 Community Oncology Conference, held April 26-27 at the Gaylord National Resort & Convention Center in National Harbor, Maryland, practice administrators from 2 community clinics discussed the changes they made to their practices to accommodate the reporting requirements and the follow-ups they have planned as they work to implement changes.

The panel, moderated by Robert Baird, Jr, RN, MSA, CASC, CEO, Dayton Physicians Network, included Alti Rahman, MHA, MBA, CSSBB, practice administrator, Oncology Consultants, and Anne Marie Rainey, MSN, RN, CHC, compliance and quality control officer, Clearview Cancer Institute.

When queried on how their practices accommodated participation in OCM, Rainey said that as with any new program, “You think it’s going well some days, but on other days you don’t.” She explained that while there are a lot of positives to participating in OCM, “We have had to also work to make changes to make this sustainable for our practice—not just

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RAINEY

OCM, but other reporting requirements as well.”

For Oncology Consultants, the initial challenge was the review of the entire quality reporting aspect within their practice. “We developed 2 teams: the first looked at the clinical data and the second focused on quality aspects,” Rahman said. The leads of the 2 teams made sure that operational changes matched the reporting, Rahman said, “which helped meet the OCM reporting and quality initiatives across our primary and satellite sites.”

According to Rainey, an open-door policy and an emphasis on communication have been keys to success. “We found out early on that in addition to e-mail updates, monthly and quarterly meetings worked well to provide continuous quality feedback for each department,” Rainey said. “We have found unique ways to make this work.” Both agreed that adequate staffing was essential to meet the quality and reporting requirements of OCM.

Challenges to Meeting OCM Requirements

When Baird asked Rainey and Rahman to identify the major challenges they have faced over the past year with OCM implementation, Rainey noted that workflow changes were the hardest barrier to overcome. The staff harbored a lot of resistance. Associates felt “we were just adding care plan steps or clicks within the workflow. That was initially huge, but we have overcome most of that, although there will

“THE PATIENT-CENTERED ASPECT OF OCM FORCED US TO COMMUNICATE MORE WITH OUR PATIENTS AND DOCUMENT THINGS THAT WERE HISTORICALLY NOT DOCUMENTED.”

—Anne Marie Rainey, MSN, RN, CHC

always be room for improvements,” she said.

she said.

Rahman identified staffing, infrastructure, and information technology needs as the challenges, a majority of which he said were related to operational and reporting requirements. Another major challenge was getting a grip on the cost of managing the manual abstraction of data from the electronic health records. “We had to look at the costs of manual versus automated data abstraction,” he said.

Constructive Lessons Learned

Rainey identified a big advantage of the patient-centered aspect of OCM.

“It forced us to communicate more with our patients and document things that were historically not documented,” she said. “For example, we were not documenting advance care directives for our patients.”

The clinic identified this as an area that needed improvement, and now 75% of their Medicare patients have these directives documented. “It can be uncomfortable for our staff as well as for patients, but we are proud that we have championed this,” she said.

Both Rahman and Rainey reiterated that communication across the various departments in their respective organizations was key to identifying problem areas and working to implement changes. Baird was curious to find out the patient feedback when informed that the clinic would be participating in a new type of reimbursement model. “We opted to mail a letter to Medicare and on-chemotherapy patients,” Rainey told the audience. While they had a lot of questions initially, they were also happy to see more information on their care plan and medications, she said.

Rahman’s practice devised a strategy to make the information about the reimbursement model more patient-friendly. “The letter can be dense, and so we created a cartoon to help patients understand their plans better. We needed to supplement the letter and explain it better,” he said.

OCM Feedback

The first wave of OCM feedback reports, for practices that had 6-month chemotherapy episodes, are out. Rainey said that while the reports were initially a bit overwhelming, she soon noticed trends as they dug deeper. “We noticed

that E&M [evaluation and management] visits were high for our practice and when we looked closer, it helped us locate an outlier physician,” Rainey pointed out. She also explained how the practice placed triage pathways in place to reduce the number of hospital and emergency department (ED) visits for patients who were troubled with nausea, vomiting, and diarrhea.

“We need to get a deeper dive into this, with the help of data analytics companies, to avoid a knee-jerk reaction so we could plan this out better,” Rainey added.

Rahman’s practice also focused on ED utilization, and their clinic was able to pinpoint the exact dollar amounts associated with patient visits to various hospitals across Houston, and the variations seen for the same treatment. “But we have to partner with analytics companies and we’d need these data more frequently,” he said.

Rahman emphasized that while his practice has extended hours, raising patient awareness to call or come to the clinic instead of visiting a hospital or the ED is vital. ♦

Congressman, Pharmacist, and Lawyer Debate PBMs, Drug Prices at Annual COA Meeting

Surabhi Dangi-Garimella, PhD



D'AMATO

WITH DRUG PRICE DEBATES ESCALATING daily, stakeholders in healthcare, particularly in cancer care, have been very vocal about who should take the blame and bring about changes to reduce the cost of care for patients. A white paper commissioned by the Community Oncology Alliance has aimed the spotlight on practices by pharmacy benefit managers (PBMs) that prevent reductions in drug prices.¹

At the 2017 Community Oncology Conference, held April 26-27 at the Gaylord National Resort & Convention Center in National Harbor, Maryland, panelists discussed the evolution of PBMs, how their role has changed over the years, and the resulting impact on drug prices and patient access.

Participating in the discussion were the Honorable Earl L. “Buddy” Carter, US House of Representatives (R-GA); Steven D’Amato, BSPHarm, executive director, New England Cancer Specialists; and Jonathan E. Levitt, Esq, founding partner, Frier Levitt. Frier Levitt helped develop the COA white paper on PBMs. Joshua Cox, PharmD, BCPS, director of pharmacy, Dayton Physicians Network, moderated the discussion.

Cox provided a historic perspective on how PBMs came to be. “In the early 1960s, PBMs played a very important role in the drug distribution network—they brought in technology that impacted the drug supply chain,” he said. Over time, however, with consolidations, their patient networks grew and PBMs played a greater role in negotiations. The Federal Trade Commission realized soon enough the conflict of interests resulting from the ensuing PBM–manufacturer alliance, and it was eventually broken up, Cox said.

Today, through mergers and acquisitions, PBMs are vertically integrated into the healthcare system, and every major PBM owns a specialty or mail-order pharmacy, Cox said, asking the panelists to comment on how they see this impact the healthcare system. »



LEVITT



CARTER

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“Escalating prices of prescription medications has shone the light on this issue with PBMs,” Carter said. It is the most talked-about topic in Congress, where lawmakers are now looking at the escalating costs and the reasons behind them, he explained, adding that “transparency is the key here.” Three PBMs controlling 80% of the market is not competition in any sense, Carter said. “We need to break that.”

He then cited the example of how pharmaceutical manufacturer Mylan, manufacturer of the EpiPen—which is used to treat life-threatening allergic reactions—was abusing the system with its EpiPen price increase.²

“PBMs are not focused on patient care, and we have access issues that we constantly face in our clinic,” D’Amato explained, adding that patient care is affected because the patients are often forced to go through a PBM to get their drug, instead of at the point of care like they provide. “On a weekly basis, my pharmacists come to me with this information,” D’Amato added, saying that PBMs are diverting prescriptions from their clinic for financial gains, which is unethical, he said.

TODAY, THROUGH MERGERS AND ACQUISITIONS, PHARMACY BENEFITS MANAGERS ARE VERTICALLY INTEGRATED INTO THE HEALTHCARE SYSTEM AND EVERY MAJOR PBM OWNS A SPECIALTY OR MAIL-ORDER PHARMACY.

Levitt explained that the PBMs’ practice of using protected health information for marketing purposes is illegal under HIPAA and under many state laws. This “prescription trolling” should not be accepted by clinics, he said. Another question that he raised was, “Where do the DIR [direct and indirect remuneration] fees gathered by PBMs go?” The power to take away 60%

to 70% profitability of a prescription is the power to exclude a community practice from the Medicare network, Levitt explained. PBMs have also tried to limit network access and pushed network terminations, he added.³

Cox asked the panelists that as clinics get a better understanding of DIR fees, “How can a pharmacy make a rational decision?” “DIR fees associated with quality metrics are not working,” D’Amato explained, adding that larger clinics might be losing millions of dollars in DIR fees. “It’s not a sustainable business model,” agreed Carter.

Levitt explained that this can ultimately impact patient access, especially when a pharmacy might be one of a few providers of certain exclusive drugs. “So, 6% DIR fees on a drug might put a pharmacy underwater,” he said.

D’Amato also indicated that a PBM cannot compete with the patient care and patient safety issues that a community practice at the point of care manages. “A PBM does not have that kind of management skill or even the relation with the patient. In my mind, we are the ones that should be providing this service,” he added.

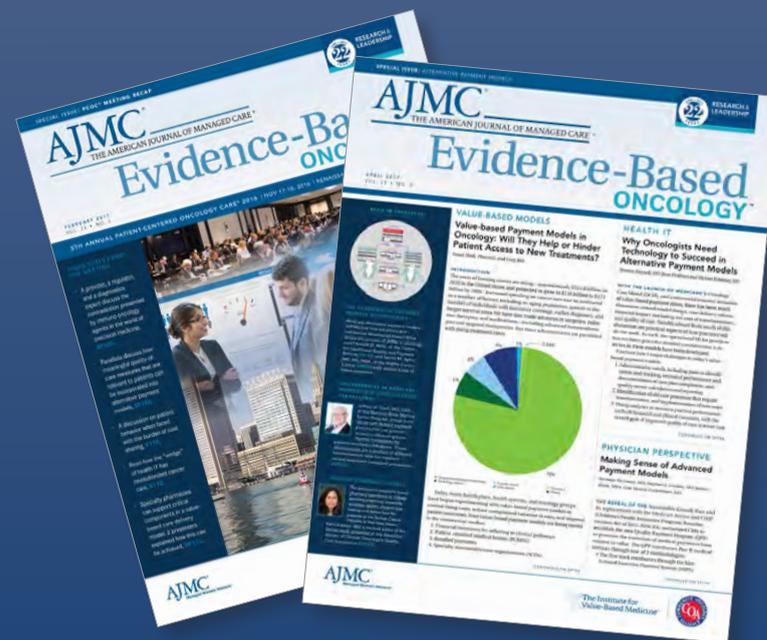
Addressing the PBM tactic of “gag orders,” whereby a PBM can prevent a pharmacy from educating patients on where they can find the drug at a cheaper price, Carter said, “We are working to eliminate this gag order.”

The panelists agreed that while PBMs have a tremendous influence on healthcare, they need to bring in more transparency. “We will continue to press on this in Congress. The executive branch is in tune with what’s going on here. We may see something evolve out of that,” Carter told the audience. ♦

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Research Tests Decision Support Technology for Guiding Cancer Screening Choices

Christina Mattina

THE RESULTS OF A NEW STUDY indicate that a technology-based intervention could help patients make informed decisions about cancer screening. The study, published in *Annals of Family Medicine*, tracked the outcomes from the implementation of a decision support module at 12 practices serving over 55,000 patients. The module was embedded in the online portals of 11,458 patients who faced an upcoming decision on breast, colorectal, or prostate cancer screening.

An initial assessment within the module gathered important information, such as patients' concerns with cancer screening, desired levels of decision support, decision-making style, and optimal method of receiving information on the recommended screening options. Using this feedback, the module created a tailored page that provided the patient's preferred amount of relevant information using words, numbers, pictures, or stories.

Patients could then indicate whether they had made up their minds on their next steps, and if so, whether they wanted their physician to receive a summary of their decision preferences that included discussion points, patient questions, and the preferred balance of decision making between the patient and the provider. Questionnaires collected feedback on the module from the patient and the clinician after the office visit during which the results were discussed.

PATIENTS WHO HAD COMPLETED THE MODULE WERE SIGNIFICANTLY MORE LIKELY TO UNDERGO SCREENING WITHIN 3 MONTHS THAN THOSE WHO HAD NOT STARTED OR COMPLETED IT.

Of the 11,458 patients invited to use the module, only 903 of the 2355 who started completed it. Around a quarter of module users clicked on at least 1 educational resource, and patients each accessed an average 3.5 resources. Patients most commonly sought information on options for getting screened (70.8%), what screening test works best (49.8%), and potential complications from screening (45.7%).

Patients who forwarded the decision summary to their physicians were more likely discuss the screening at their next visit, and 80.9% said the conversation helped reduce their fears or worries about screening. A majority of patients agreed that the module was easy to complete and understand, and sizable proportions reported that it had improved their knowledge before the office visit (48.1%) and got them more involved in the screening decision (47.7%). Finally, patients who had completed the module were significantly more likely to undergo screening within 3 months than those who had not started or completed it.

According to the researchers, these findings indicate that technology-enabled decision support initiatives are a feasible way to empower patients in decision making and help improve communication between patients and physicians. They noted that invitation response rates and module completion levels were relatively low, but could potentially increase with better workflow integration. This was also a self-selected sample without a control group, so future trials will need to be randomized and controlled to more fully evaluate the role of decision support technologies in cancer screening and other health choices.

The researchers acknowledged that implementing new technologies within practice workflows will not be an easy task, but if "future research confirms the benefits of this approach—more informed patients, better decisions, and wiser use of encounter time—the return on investment could offset the implementation costs and improve care." ♦

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Lowering the Risk of Venous Thromboembolism With Ovarian Cancer Treatment

Surabhi Dangi-Garimella, PhD

TWENTY-FIVE PERCENT OF PATIENTS receiving neoadjuvant chemotherapy treatment for ovarian cancer develop venous thromboembolism (VTE), according to the results of a new study published in the journal *Obstetrics & Gynecology*.¹

Patients with ovarian cancer have historically been associated with developing VTE. Significant risk factors include obesity, older age, advanced disease stage, debulking surgery, and use of anticoagulants. Development of this hematological condition can, in turn, lead to a poor prognosis or a reduced quality of life for patients. Although postoperative efforts have focused on reducing the incidence of thromboembolic events in women with ovarian cancer, the 4-week standard treatment that is currently offered may not be sufficient to reduce the long-term risk.²

With the hypothesis that neoadjuvant chemotherapy increases the incidence of VTE, the authors of the current study conducted a retrospective analysis among 112 patients with ovarian cancer who were being treated with neoadjuvant chemotherapy. Thirteen patients who presented with a symptom of VTE were disregarded prior to analysis. Thirty of the 112 patients at risk (26.8%; 95% CI, 19.3%-35.9%) experienced a VTE. Thirteen patients (11.6%; 95% CI, 6.8%-19.1%) experienced this hematological event during the neoadjuvant chemotherapy treatment, 6 (5.4%; 95% CI, 2.4%-11.5%) developed the condition postoperatively, and 11 (9.9%; 95% CI, 5.5%-17%) developed VTE during adjuvant chemotherapy.

Based on these findings, the authors confirm that neoadjuvant chemotherapy positions patients with ovarian cancer at an extremely high risk of developing VTE. Highlighting the importance of prophylactic treatment in preventing the incidence of VTE, they note that prophylaxis could improve survival in this patient population. This is especially important because of the rapidly growing population of patients with ovarian cancer who are administered neoadjuvant chemotherapy in the United States, they write. ♦

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Pembrolizumab Plus Chemotherapy Approved for Metastatic Nonsquamous NSCLC

Surabhi Dangi-Garimella, PhD

TUMOR RESPONSE RATE AND progression-free survival (PFS) were the benchmarks that helped pembrolizumab (Keytruda) gain accelerated approval as first-line treatment for metastatic nonsquamous non-small cell lung cancer (NSCLC) in combination with pemetrexed (pem) and carboplatin (carbo), irrespective of PD-L1 expression.

Observations in a subpopulation of patients who were part of the KEYNOTE-021 trial led to the new approval. A cohort of 123 treatment-naïve patients with metastatic nonsquamous NSCLC, with no mutations in *EGFR* or *ALK* genes, were treated with pembrolizumab plus pem/carbo or pem/carbo alone. Including pembrolizumab in the treatment regimen improved the objective response rate from 29% (95% CI, 18%-41%) to 55% (95% CI, 42%-68%). Further, a majority of patients (93%) who received pembrolizumab had a duration of response that was »

at least 6 months (range, 1.4+ to 13+ months) compared with 81% of patients who did not (range, 1.4+ to 15.2+ months). Pembrolizumab also improved the median PFS by about 3.1 months.

With respect to adverse events, pembrolizumab treatment resulted in pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis. Pembrolizumab can also cause severe or life-threatening infusion-related reactions.

“This approval marks an important milestone in the treatment of lung cancer. Now, pembrolizumab in combination with pemetrexed and carboplatin can be prescribed in the first-line setting for patients with metastatic nonsquamous non-small cell lung cancer, irrespective of PD-L1 expression,” said Corey Langer, MD, director of thoracic oncology and professor of medicine at the Hospital of the University of Pennsylvania.¹ Langer emphasized that physicians should consider individual patient characteristics, such as biomarker status, histology, and other clinical factors, to carve out an appropriate treatment plan.

The approval of pembrolizumab as first-line therapy, alone or in combination with chemotherapy agents, has opened up the horizon’s for Merck, the company that developed the molecule. More than 200,000 individuals are diagnosed annually with NSCLC in the United States.² The drug spend will be an issue, however: the combination of pembrolizumab and chemotherapy will cost more than \$250,000 annually. ♦

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USPSTF: Do Not Screen for Thyroid Cancer in Asymptomatic Individuals

Surabhi Dangi-Garimella, PhD

THE US PREVENTIVE SERVICES TASK FORCE (USPSTF) has provided a D recommendation (discourages the use of service) for thyroid cancer screening in asymptomatic individuals.

Thyroid cancer incidence has increased nearly 3 times over a 40-year period: 15.3 cases per 100,000 persons in 2013 compared with 4.9 cases per 100,000 in 1975. However, mortality rates have not seen much of a spike, increasing by just 0.7 deaths per 100,000 persons each year. It’s also important to note that the 5-year survival for the disease ranges from 99.9% for localized disease to 55.3% for individuals who have metastases.

The USPSTF revisited neck palpation or ultrasound as a screening technique used in asymptomatic individuals to evaluate its impact on health outcomes. The recommendations, however, do not apply to individuals with hoarseness, pain, difficulty swallowing, or other throat symptoms or persons who have lumps, swelling, asymmetry of the neck, or other reasons for a neck examination. They also do not apply to persons at increased risk of thyroid cancer because of a history of exposure to ionizing radiation, particularly persons with a diet low in iodine, an inherited genetic syndrome associated with thyroid cancer, or a first-degree relative with a history of thyroid cancer.

The USPSTF committee found no direct evidence that compared screened versus unscreened populations or immediate surgery versus surveillance or observation that showed an impact on health outcomes, such as mortality, quality of life, or harms. “The USPSTF found inadequate direct evidence on the harms of screening, but determined that the magnitude of the overall harms of screening and treatment can be bounded as at least moderate, given adequate evidence of harms of treatment and indirect evidence that overdiagnosis and overtreatment are likely to be substantial with population-based screening,” the authors noted.

The research, according to the report published in *JAMA*, points to the need for observational studies of early treatment versus surveillance or observation of patients with small, well-differentiated thyroid cancer to identify patients at highest risk for clinical deterioration. The experts also noted the absence of risk prediction tools or biomarkers to understand the prognosis of differentiated thyroid cancer.

While there is no direct evidence proving that screening for thyroid cancer can result in overdiagnosis, the fact that increased incidence has not resulted in increased mortality is telling, according to the report. “Overdiagnosis occurs because screening for thyroid cancer often identifies small or slow-growing tumors that might never affect a person during their lifetime,” committee member Seth Landefeld, MD, said in a statement for USPSTF. “People who are treated for these small tumors are exposed to serious risks from surgery or radiation, but do not receive any real benefit.” ♦

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Screening Rate Disparities for Some Cancers May Have Decreased After ACA, Study Finds

Christina Mattina

ACCORDING TO A NEW STUDY, although socioeconomic disparities in mammography rates among Medicare beneficiaries decreased after the implementation of the Affordable Care Act (ACA), the same pattern was not observed for colonoscopies. The researchers hypothesize that the free preventive services required under the ACA may have removed cost as a barrier, but other obstacles to cancer screening persist.

The study, published in *Cancer*, looked at 2 samples of Medicare beneficiaries aged 70 or older and determined whether they had received the recommended cancer screening based on the date of their most recent preventive mammography or colonoscopy. They also collected information on patients’ cancer risk factors and county-level income and education data. The mammography analysis included a sample of over 862,000 women, and the colonoscopy sample included over 326,000 men and women.

The researchers explained that the ACA’s provision eliminating out-of-pocket costs to patients for preventive services was intended to expand access to screening and reduce disparities, but few studies had compared screening rate changes after the ACA. Thus, their study conducted analyses to compare screening rates and their relation to income and education factors in the 2-year period before the ACA was implemented (2009 to 2010) and the 2-year period after implementation (2011 to 2012).

For the mammography group, the researchers found an association between lower socioeconomic status and decreased mammography rates, both before and after the ACA, but the disparities decreased significantly after the law’s implementation. The odds ratio for the women in the lowest-income quartile receiving a mammogram compared with those in the highest quartile increased from 0.87 to 0.94 after the ACA, while the corresponding odds ratios for education quartiles increased from 0.76 to 0.86. From the pre-ACA period to the post-ACA period, the researchers found that mammography rates increased within each quartile of income and education.

In the colonoscopy analysis, however, the researchers observed a slight decrease in colonoscopy rates after the ACA was implemented, finding there were no significant changes in the associations between socioeconomic indicators and screening rates over the study period. “The interaction tests indicate that the effects of income, education, and quartile did not differ significantly be-

tween the 2 time periods,” the authors wrote, acknowledging that they could not establish a causal relationship between the ACA and screening rates.

They wrote that the mammography findings indicated that the financial cost of preventive services may have been a potential obstacle to cancer screening, but it is far from the only factor. “The findings support the removal of out-of-pocket expenditures as a barrier to the receipt of recommended preventive services, but emphasize that for colonoscopy, other factors such as a fear of sedation, perceived discomfort, and a need for bowel preparation should be considered,” they concluded.

The researchers also suggested that further studies be undertaken to assess the effects of the ACA on screening rates among other populations, such as people who gained insurance coverage under the law. ♦

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Avalere and FasterCures Release Patient-Perspective Value Framework 1.0

Surabhi Dangi-Garimella, PhD

A YEARLONG COLLABORATION BETWEEN a health consultancy and a think tank has resulted in the first draft of a framework that considers the value of healthcare services from the patient’s perspective—the Patient Perspective Value Framework (PPVF).

Avalere Health and FasterCures, a center of The Milken Institute, initiated a collaboration in June 2016 to develop the PPVF. The objective was to incorporate the framework, or parts of it, into existing value framework platforms, including the American Society of Clinical Oncology (ASCO)’s Value Framework,¹ the

“AS THE US HEALTHCARE SYSTEM TRANSITIONS TO VALUE-BASED PAYMENT, IT IS IMPERATIVE THAT WE GET THE VALUE DEFINITION RIGHT AND MEASURE WHAT TRULY MATTERS TO THE PATIENT.”

—Josh Seidman

Institute for Clinical and Economic Research (ICER)’s Value Assessment Framework,² and the National Comprehensive Cancer Network (NCCN)’s Evidence Blocks.³

The 2 organizations convened multiple stakeholders to steer the development of PPVF, including patient groups (Cancer Support Community, Leukemia & Lymphoma Society, Michael J Fox Foundation, and National Multiple Sclerosis Society), healthcare think tanks (FasterCures, National Health Council, Partnership to Improve Patient Care, and

Patient-Centered Outcomes Research Institute), payers (Aetna and CVS Health), pharmaceutical developers and their representatives (Amgen, Astellas Pharma, Biogen, Edwards Lifesciences, Gilead Sciences, GlaxoSmithKline, Johnson & Johnson, Pharmaceutical Research and Manufacturers of America, and Sanofi), and others (American Heart Association and Better Medicare Alliance).

“As the US healthcare system transitions to value-based payment, it is imperative that we get the value definition right and measure what truly matters to the patient,” Josh Seidman, senior vice president in Avalere’s Center for Payment and Delivery Innovation, said in a statement.⁴ He believes that PPVF can assist healthcare organizations integrate what matters to patients in their payment models.

There are 5 components that reside within this framework:

- **Patient preferences.** This domain, which assesses a patient’s personal goals and preferences, weighs 3 other domains of the PPVF: patient-centered outcomes, patient and family costs, and quality and applicability of evidence.



Stakeholders Define Value in Healthcare

The American Journal of Managed Care® (AJMC®) invited a panel with diverse expertise and opinions to share a platform: the Oncology Stakeholders Summit.

Panelists, representing health plans, the pharmaceutical industry, and patient advocacy, examined the strengths and weaknesses of existing calculators and reached consensus on additional considerations that are relevant across stakeholder groups.

You can access the discussion here: www.ajmc.com/link/1913.

It measures the patient’s values, needs, goals/expectations, and financial tradeoffs.

- **Patient-centered outcomes.** This domain assesses the clinical, functional, and quality of life benefits and drawbacks of various healthcare options for the patient.
- **Quality and applicability of evidence.** This domain evaluates the strength and consistency of evidence and its relevance for an individual patient.
- **Patient and family costs.** This domain uses insurance benefit design and patient-reported data to calculate the medical, nonmedical, and future costs of healthcare options for the patient and their family.
- **Usability and transparency.** To ensure usability of the framework for the intended audience and assess the transparency of the framework’s approach, this domain determines how the weighted assessments of the other domains will be communicated through a specific application.

The developers of the PPVF envision using this framework for shared decision-making, incorporating it within existing value frameworks, supporting public health programs, and to inform patient-centered drug development.

Future plans include collaborating with other framework developers, and to that effect, representatives from ASCO, ICER, NCCN, and Memorial Sloan Kettering’s DrugAbacus participated in a meeting with PPVF’s steering committee to discuss potential opportunities for collaboration.

The next phase of the initiative is expected to kick off in June 2017. ♦

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Produced by Laura Joszt

Allison Silvers on Payment Model Flexibility in Palliative Care

Fee-for-service payment models have not been successful in the field of palliative care, where small practices seem to work better under flexible programs like per member per month, said Allison Silvers, vice president of payment and policy at the Center to Advance Palliative Care.



What are some payment models that have successfully increased access to palliative care?

What we've found is that the fee-for-service model clearly does not work for palliative care. Too much time is needed by the professionals,

and there are all the "unbillable" professionals. The payment model that seems to give the most flexibility is per member per month, especially for home-based palliative care where the program is taking care of a specific population. The problem with other models such as fee-for-service with shared savings is that the shared savings are too remote and several programs are small and unwilling to take risk. So just having enough of a flexible pot of money seems to work best.

How have your experiences with community health shaped your work with the Center to Advance Palliative Care?

I spent many years running a senior information center where older adults in need would just come in, it was a storefront, and they would need help with housing or social services or finding good care. It was a really good flavor of people not knowing what their options are, and I think that same thing is true for palliative care. Obviously, there's a lot of emotional turmoil associated with getting diagnoses, and your doctor then informs you of what they recommend.

Typically, there's a whole menu of treatment options, and that's not adequately communicated, and there's also a lot of other needs that you have that wouldn't even be addressed with treatment: spiritual needs, family reconciliation needs, etc. I think that idea of giving people options and helping them think through their options is what's common.

Daniel J. Klein Outlines Patient Routes to Accessing Costly Medications

According to Daniel J. Klein, president and CEO of the Patient Access Network (PAN) Foundation, patients now have an easier time accessing the high-cost treatments they need, thanks to certain policies and programs. Klein also anticipates that a recently enacted law will bring down the prices of some prescription drugs.



What are the major ways patients can get access to costly medications?

Today, most patients do have some form of health insurance, which is great. Usually, there's coverage available for even high-cost medications through the various health

insurance plans that patients have. Where it becomes challenging is when the health insurance plan may have a high deductible, or copay, or coinsurance, and in that case, some patients need additional assistance.

Many patients rely on assistance from the drug manufacturer in the form of a coupon or a co-pay card. Then, patients, particularly in Medicare and other federal insurance programs, may need to come to a charitable assistance program, like the PAN Foundation. But, by and large, as a result of the Affordable Care Act and the expansion of Medicaid, most people do have access to the treatment that they need.

What impact do you expect the 21st Century Cures Act to have on improving access to medications?

Clearly, the process for approving generic drugs has been slower than most people would like. The high cost of some drugs may be reduced through competition through generics, so I think that there's every reason to hope that the 21st Century Cures Act will improve affordability of at least some medications, and in turn improve access.

The Samfund Expands Its Scope With Financial Literacy Initiatives, Says Samantha Watson

The Samfund is primarily known for its grant funding programs that help young adults struggling financially after having cancer, but founder and CEO Samantha Watson discussed how the organization has expanded into providing financial literacy education and other tools to support the community of cancer patients.



What are some of The Samfund's initiatives to support young adults who are struggling financially due to cancer?

At the Samfund, our biggest program has always been a grants program. We've awarded just over \$1.7 million in grants over the last decade. A lot of

what we fund is basic everyday stuff, so we provide some help with medical bills and copays and things like that, but we also help with rent and mortgage. We help with insurance premiums, and we help with car payments, and we help with anything that becomes a hardship because someone has gone through cancer at a young age.

But we have also started to focus on financial education, on encouraging some of these conversations, and on helping to improve communication around finances. We have launched a program called Finances 101: A Toolkit for Young Adults with Cancer, which is an online decision-making guide.

The first topic that we covered, right at the time when open enrollment started, was around choosing a health insurance plan, because what we see in our grants program, for example, is that young adults are on their own for insurance for the first time. The marketplace is confusing, and they only have enough, they think, to cover the cheapest monthly plan. So, they get the cheapest monthly plan and then they can't see their doctors because the plan doesn't cover them, or they're going bankrupt because their deductible was way higher than they realized.

We created this guide to help them figure out how to calculate the full cost of insurance for the year, how to compare plans, what their options are, when their marketplace opens, and how to navigate the site. It's meant not to give directive advice about which plan they should pick, but to put them back in the driver's seat when it comes to being informed and picking the best plan for them.

From there, we're going to build out to other topics and really explore this world of financial education and financial literacy, because we think, our hunch after the thousands upon thousands of applications that we've read over the years, that a lot of these financial crises can be prevented if people have better information and guidance along the way, and especially at those critical decision-making points. If they're armed with information, then hopefully they won't panic, and hopefully they won't make a decision that's going to affect them negatively in the long run.

It also opens up the community that we're able to support, because for years we've focused on young adults once they're finished with treatment. For the toolkit and for our webinar series which also provides a similar type of guidance and support, we don't care how old someone is if they access it. We don't care what their treatment status is. We don't have to care about any of that. We can put the information out and hope that it's helpful. It really also, again, opens up the type of support that we provide and the size of the community that we're able to support. ♦

PROVIDER PERSPECTIVE

Project ECHO: An Effective Means of Increasing Palliative Care Capacity

Sanjeev Arora, MD; Tracy Smith, BS; Jennifer Snead, PhD; Sarah Zalud-Cerrato, MPH; Lisa Marr, MD; Max Watson, MBChB; Sriram Yennu, MD; Amy Bruce, MPP; Chris Piromalli, DO; Stacy Kelley, MPH; Nandini Vallath, MD; Gabriela Píriz, MD; Gabriel Sehabiaga, MD; and Alvaro Méndez, MD

continued from cover

and end-of-life care—can provide symptom control, psychosocial support, and coordinated transitions of care for patients and their families.³⁻⁵

Yet, as Atul Gawande, MD, MPH, documented in his 2010 book, *Being Mortal*, best practices and innovations in creating or maintaining quality of life (QOL) for individuals nearing the end of their lives, or faced with life-threatening conditions, are not readily accessible to those who need them most.⁶

Despite ongoing efforts to incorporate palliative care concepts and training in medical and nursing education,⁷ barriers to access persist, and palliative care remains an insufficiently researched topic.⁸ The World Health Organization estimates that 19 million adults across the world are in need of palliative care, the majority in low- and middle-income countries, but that in many areas, the level of palliative care provision and access to services remain extremely limited and clinicians often lack the capacity to provide care to all in need.⁹

In the United States, large regional disparities in access to palliative care exist, especially in rural areas and among medically underserved populations.¹⁰ The number of palliative care specialists falls far short of demand, exacerbating geographic, racial, and economic disparities in access.^{11,12} Culture- and country-specific assumptions, perceptions, and laws about palliation, pain relief, and drug prescription/use are also significant impediments to effective palliative treatments.¹³

To overcome the gap between the growing need and the limited resources for palliative care around the globe, a transformative educational intervention is necessary. Such an innovation must effectively disseminate the principles, best practices, and applications of palliative care concepts for the frontline healthcare practitioners who serve communities most in need of that care. For the past 14 years, Project ECHO (Extension for Community Health Outcomes) has leveraged its innovative technology-enabled model for healthcare education to address global disparities in healthcare access for complex chronic conditions such as hepatitis C, HIV, tuberculosis (TB), and opioid use disorder. The ECHO model, which fosters and sustains communities of practice that bring together primary care clinicians with interdisciplinary specialist teams for ongoing case-based learning, mentoring, and sharing of best practices, also has the potential to tip the scales of the world's integrated palliative care crisis. This article describes the work of 7 of Project ECHO's replicating partners from around the world who are implementing the ECHO model to address the knowledge gap that underlies this crisis.

Project ECHO

Project ECHO improves healthcare workforce capacity and increases access to specialty care for the world's rural and underserved populations. A low-cost, high-impact intervention, Project ECHO links expert multidisciplinary specialist teams with frontline community healthcare providers via ongoing videoconference-enabled sessions. In these teleECHO clinics, specialists share their expertise and community providers share their experience with individual patients via case-based learning and telementoring. Overall knowledge is enhanced as cutting-edge research, treatments, and

best practices from academic and research centers are tested and refined through ongoing discussion and application within community- and culturally-specific contexts on the ground. Participating community providers do not need any additional equipment to participate other than a laptop enabled with internet and a video-camera. The ECHO model builds and strengthens communities of practice through latitudinal learning and the free exchange of knowledge: all participants teach, and all participants learn from one another. Community providers develop the capacity to care for patients with complex conditions where they live.

Project ECHO benefits not only patients in need of care, but also the providers who care for them. The communities of practice built through regular teleECHO clinics reduce professional isolation for providers located in rural areas, building networks and new opportunities for collaboration.¹⁴⁻¹⁷ These additional resources and opportunities support clinic staff retention and increase professional satisfaction.¹⁸⁻²¹ The peer support and mentorship that teleECHO clinics provide enable critical incident stress debriefing and self-care strategies, reducing provider burnout.

Project ECHO moves knowledge, not patients (**Figure 1**). It provides increased access to high-quality healthcare and reduces travel to, and wait times at, centers of medical expertise. The ECHO model, originally designed and implemented in 2003, addressed the lack of hepatitis C care across rural New Mexico. Within 18 months of establishing the first teleECHO clinic sessions, which connected primary care providers and community health workers around the state with a multidisciplinary specialist team at the University of New Mexico (UNM), wait times at the UNM hepatitis C clinic had dropped from 8 months to 2 weeks. Rural providers reported a greater sense of self-efficacy and confidence in treating hepatitis C patients in their own communities. Subsequent research demonstrated that the cure rate of those providers was the same as that in the UNM hepatitis C specialty clinic.¹⁴

Fourteen years later, Project ECHO has grown from 1 program serving rural New Mexico to over 110 partners in over 20 countries addressing over 55 conditions. The ECHO model has proved effective for hepatitis C treatment in the US Department of Veterans Affairs,¹⁵ for training primary care providers in the provision of buprenorphine for treatment of patients with opiate use disorder,¹⁶ and improvements in clinician geriatric mental healthcare knowledge/treatment and decreases in emergency room costs for their patients with mental health diagnoses.¹⁷ Providers participating in teleECHO clinics regularly report increased professional satisfaction and a reduced sense of isolation, along with improved self-efficacy and capacity to care for their patients.¹⁹⁻²¹ Globally, the ECHO model is being deployed in Europe, Asia, Africa, and India to expand frontline health workers' capacity to care for underserved populations across complex chronic conditions »



ARORA

Sanjeev Arora, MD, is director of the ECHO Institute and distinguished professor, University of New Mexico.

SPECIALISTS IN TELE-ECHO CLINICS SHARE THEIR EXPERIENCE WITH INDIVIDUAL PATIENTS VIA CASE-BASED LEARNING AND TELEMENTORING.

TABLE. Palliative Care ECHO Projects

Organization Name (type)	Funding Streams	Hub Structure (number of individuals, type of professions)	Spokes (number of individuals, type of professions)	Time Period	Curriculum (number of sessions, case presentations by spokes, etc)
University of New Mexico (AMC)	Philanthropic grant	Members of the palliative care consultation service at UNMH, with physicians; social workers; chaplains; advance practice nurses, guest participants in the community; and learners, including medical students, residents, and fellows.	Community participants include physicians, physician assistants, advance practice nurses, nurses, pharmacists, social workers, chaplains, and psychologists.	2011-2014	1.5 hours biweekly; 15-month curriculum in 6 categories: introduction to palliative care, communication techniques, pain assessment and management, non-pain symptom management, psychosocial issues, and special topics
	Legislative allocation		Nonspecialists of all disciplines.	New session, Fall 2017-ongoing	1 hour weekly over lunch; 12-month curriculum focused on primary palliative care knowledge and skills
Northern Ireland Hospice/Health and Social Care Board (hospice/government)	Government of Northern Ireland	Composition varies across multiple ECHOs addressing palliative care issues.	Caregivers, nurses, home healthcare staff, nursing home staff, assisted living staff, pain care teams, and prison healthcare teams.	November 2014-ongoing	Varied; see echonorthernireland.co.uk/
Servicio de Medicina Paliativa, Hospital Maciel/Universidad de la República/ Administración de Servicios de Salud del Estado, Uruguay (AMC)	Government of Uruguay	Members of the palliative care unit of Maciel Hospital, including doctors specializing in palliative care, nurses, social workers, psychologists, and the ECHO technical team.	Professionals from all over the country participate: physicians, family doctors, general practitioners, nurses, social workers, and psychologists.	August 2015-ongoing	1.5 hours biweekly; 2 clinical cases per meeting are discussed
ResolutionCare Institute; 501(c)(3) not for profit	Partnership HealthPlan of California (Medicaid MCO), California Healthcare Foundation, local foundations, and individual donors	Palliative care specialty interdisciplinary team plus national palliative care leaders as guest faculty throughout the pilot.	Primary care teams in Federally Qualified Health Centers and Indian Health Services clinics.	September 2015-June 2016	1.5 hours biweekly
University of Texas MD Anderson Cancer Center (AMC)	Sister Institution Network Fund	Faculty specialists at MD Anderson Cancer Center Department of Palliative Care, Rehabilitation, and Integrative Medicine.	Palliative care clinicians, primary care physicians, mid-level providers, nurses, technicians, and community health workers. Collaborators in South Africa, Zambia, Kenya, Nigeria, Ghana, Brazil, and Mozambique.	May 2016-ongoing	1 hour bimonthly
Alaska Native Tribal Health Consortium; 501(c)(3) not for profit	Alaska Native Tribal Health Consortium institutional support	Led by palliative care specialty interdisciplinary team, including outpatient and inpatient providers as well as rural healthcare providers and interested staff across the Alaska Tribal Health System.	Rural healthcare providers, medical staff, and community members.	Spring 2017-ongoing	Primary palliative care with a goal of establishing regional palliative care resource teams throughout the state to offer primary palliative care support to patients and families facing advanced serious illness.
Trivandrum Institute of Palliative Sciences (AMC)	ECHO India Trust	Members of the multi-disciplinary team at Trivandrum Institute of Palliative Sciences comprising physicians, nurses, medical social workers, psychiatrists, psychologists, and needs-based specialists.	Hospital-based practitioners, nongovernment organization representatives, and private and governmental palliative care providers.	January 2017-ongoing	2.5 hours biweekly, including case discussion and didactic presentations within a 6-month curriculum on the theme "Treat that Pain."

AMC indicates academic medical center; ECHO, Extension for Community Health Outcomes; MCO, managed care organization; UNMH, University of New Mexico Hospital.

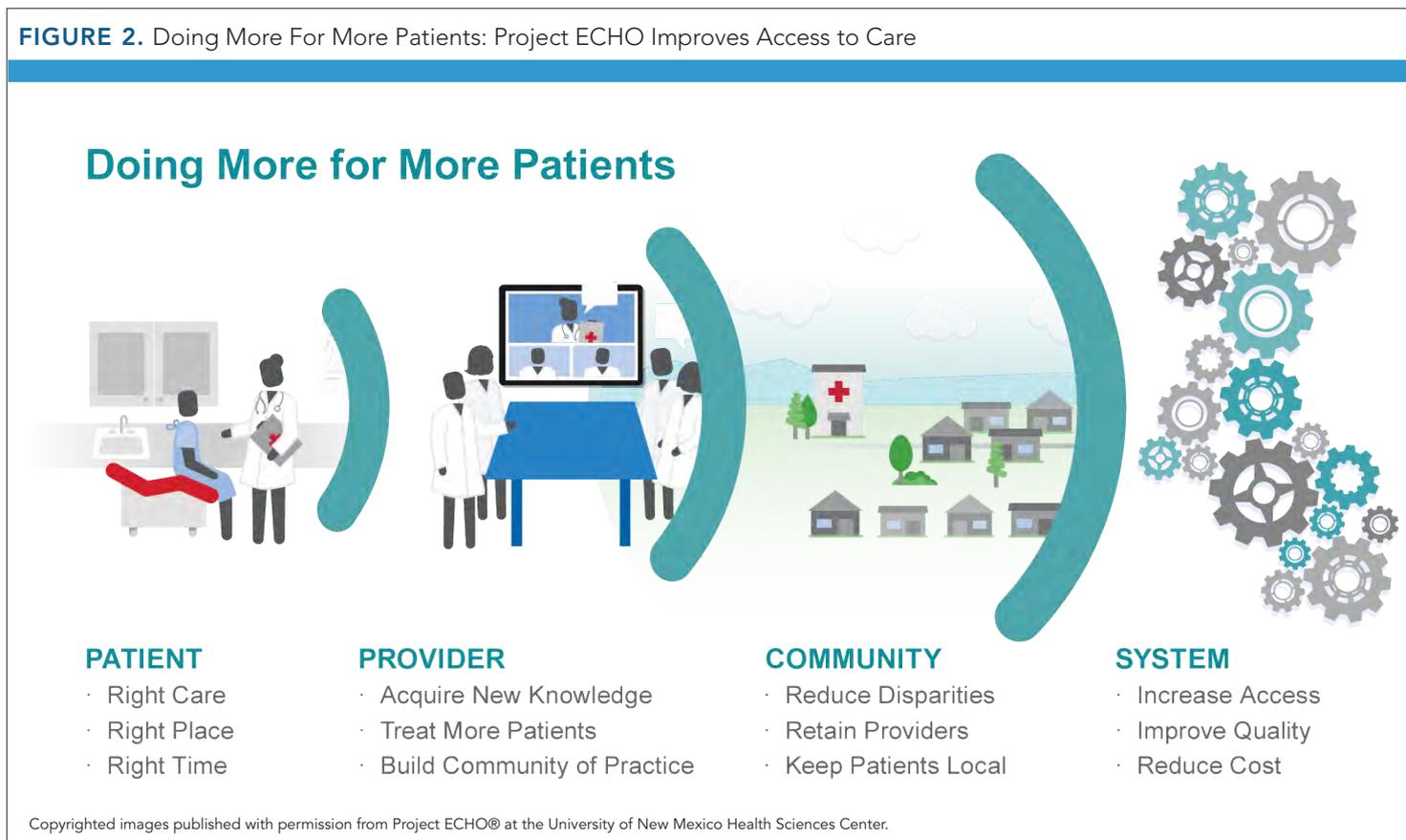
like HIV, cancer, hepatitis C, multidrug-resistant TB, and behavioral health.

Project ECHO provides a unique model to address global disparities in access to palliative care. The ECHO model has been replicated by early adopters to expand, support, and disseminate knowledge of primary palliative care to providers working with rural and underserved populations, enabling them to address the complex needs of their patients with advanced serious illness. In its focus on ongoing mentorship and development of multidisciplinary communities of practice, the ECHO model is particularly suited to palliative care, which at its best involves care teams supporting patients and their families in the transition

from medical support for a specific condition to a focus on overall QOL. Each of the brief narratives below recounts the experience of implementing ECHO for palliative care from the perspective of 7 of our replicating partners (also, see **Table**).

The UNM Experience

The UNM Hospital started the first palliative care teleECHO clinic in 2011. Pre- and post-surveys of participants have demonstrated improved self-efficacy ($P = .0073$) and greater knowledge of pain and non-pain symptom management with participation ($P = .0156$).²² In the fall of 2017, a new session of the UNM Palliative Care ECHO will begin, this time with a focus on primary pal-

FIGURE 2. Doing More For More Patients: Project ECHO Improves Access to Care

liative care for non-specialists of all disciplines. In preparation for this next phase, members of the teleECHO clinic specialist team are traveling around the state to conduct needs assessments and discuss potential benefits of this clinic with nonspecialists.

Northern Ireland Hospice

Northern Ireland Hospice first implemented ECHO for palliative care in 2014 under the leadership of medical director Max Watson, MD. Community hospice nurses (CHNs) who were employed reported that ECHO created a safe space for those working in isolation to talk about and learn from failures and successes in their own work, and to support each other. The original 6-month pilot was evaluated using a mixed-methods prospective longitudinal cohort study involving 28 CHNs. Mean knowledge scores improved significantly, as did overall self-efficacy scores. Seventy percent of CHNs reported that the technology used in ECHO had given them access to education that would have been hard to access due to geography. The study provided evidence for Project ECHO-connected networks of CHNs as an affordable solution to the United Kingdom's growing need for hospice and palliative care. The Northern Ireland Hospice has become an ECHO superhub, and in partnership with the Health and Social Care Board of Northern Ireland, has launched 19 different teleECHO clinics, many of which address integrated palliative care.

ResolutionCare

Northern California-based ResolutionCare launched a palliative-care-to-primary-care teleECHO pilot program in September 2015. Working with Partnership HealthPlan of California, a non-profit healthcare organization contracted with the State of California to administer Medi-Cal benefits, ResolutionCare implemented the ECHO model to provide hospice and palliative medicine training to primary care teams at 10 federally qualified health centers throughout Northern California.²³ In addition to using ECHO for developing palliative care curricula and networking community partners with physicians and other healthcare professionals, ResolutionCare's pilot explores value-based systems of pay-

ment. After April 2017, when California Senate Bill 1004 on Palliative Care goes into effect, standardizing value-based systems statewide, the ResolutionCare's pilot program will become an ongoing initiative to address California's exploding demand for palliative care.²⁴

Uruguay

The palliative care service of Montevideo's Hospital Maciel in partnership with Universidad de la República, started a palliative care teleECHO clinic in August 2015. Prior to this, the ECHO model had been implemented to train hepatitis C providers in Uruguay. The palliative care teleECHO clinic for adults created an interdisciplinary network of health professionals who assist patients in advanced or terminal stage of their disease throughout the country. Multidisciplinary specialist teams collaborate with providers in comprehensive patient and family assistance, collective decision-making, and a holistic, QOL approach to patient care. Watson, of ECHO Northern Ireland, traveled to Uruguay during the initiative's planning stages to engage local providers, share best practices for utilizing the ECHO model for hospice and palliative care, and learn about how palliative care is practiced in Latin America. Watson's mentorship at the beginning of the teleECHO palliative care clinic in Uruguay further demonstrates the collaborative potential of the global ECHO network.²⁵

MD Anderson Cancer Center

In May of 2016, the Department of Palliative Care, Rehabilitation, and Integrative Medicine at the University of Texas MD Anderson Cancer Center launched its Palliative Care ECHO Telementoring Program (ECHO PACA) in collaboration with clinicians in South Africa, Zambia, Kenya, Nigeria, Ghana, Brazil, and Mozambique. ECHO PACA's goal is to build a network of palliative care experts »

OVER 14 YEARS, PROJECT ECHO HAS GROWN FROM 1 PROGRAM SERVING RURAL NEW MEXICO TO OVER 110 PARTNERS IN OVER 20 COUNTRIES ADDRESSING OVER 55 CONDITIONS.

ADDITIONAL RESOURCES

OncLive

Hear about the palliative care program offered at the University of Chicago from Stacie Levine, MD: onclive.com/link/1177.

in Africa, connecting experts and providers through the ECHO model to provide increased access and quality palliative care for patients with life-limiting cancer diagnoses.²⁶

Alaska Native Tribal Health Consortium

The Alaska Native Tribal Health Consortium (ANTHC) in Anchorage is America's largest and most comprehensive Native-owned health services organization. It serves over 150,000 Alaska Native people statewide, representing 229 federally recognized tribes. Through the Alaska Native Medical Center, ANTHC began offering oncology-based comprehensive palliative care services in October 2015 and launched a palliative care teleECHO clinic in the spring of 2017, extending palliative care services to inpatient, outpatient, and rural settings across the Alaska Tribal Health System. Project ECHO will enable ANTHC and tribal partners to utilize existing resources to support patients, families, providers, and communities throughout Alaska, providing support and mentorship for the development of community-based palliative care resources. The goal of the ANTHC Palliative Care Project ECHO is to establish regional palliative care resource teams throughout the state to offer primary palliative care support to patients and families facing advanced serious illness.

Trivandrum Institute of Palliative Sciences

In India, the Trivandrum Institute of Palliative Sciences (TIPS) implemented the ECHO model for palliative care in January of 2017. This teleECHO clinic aims to strengthen the palliative care knowledge and capacity of practitioners from India and neighboring countries (including Nepal, Bhutan, and Bangladesh). TIPS conducts its teleECHO clinic with technological support and guidance from the Project ECHO superhub team based in Delhi, further evidence of the capacity of the global ECHO network to provide mentorship and support across regions and conditions.²⁷

The ECHO Institute in Albuquerque, New Mexico, is also leading a Palliative Care ECHO Collaborative, a broader community of practices that connects all ECHO replicating partners working in palliative care to share best practices and strategies for addressing the global palliative care crisis. The collaborative is exploring opportunities to engage in collective research and the development of a palliative care curriculum and certification that can be standardized for primary care clinicians and other healthcare providers around the world. Delivered through the culturally adaptive ECHO model, this curriculum and certification could then be effectively modified by palliative care ECHO teams working in diverse geographic areas to suit the specific needs of participants.

The network of palliative care practitioners, researchers, and interested partners built by the Palliative Care ECHO Collaborative would also shape the development of best practices and serve as a catalyst to raise awareness about global palliative care needs. Such conversations are already well underway: in India, for instance, the ECHO model has become useful for conversations with the oncology community regarding the scope of palliative care across the cancer spectrum. India's National Cancer Grid, which connects 106 cancer centers,²⁸ has included palliative care experts in its ECHO virtual tumor board. The engagement and dialogue among participants opens up possibilities for mutual learning and further collaborations in transforming quality of care provided and perceived.

Conclusion

There is growing national and international interest in palliative care but a recognized inability for specialists to provide such care to the patients and families who need it most. Project ECHO is an effective

solution to the problem of disseminating the skills and expertise of centralized palliative care specialists to the frontline primary care providers working in geographically, culturally, and economically diverse communities.

The ECHO model can assist healthcare providers, medical staff, and community members to acquire new skills, competencies and best practices in palliative care. By working with administrators and community leadership, efforts to improve the QOL and coordination of care for patients with advanced serious illness will also help identify and address local, national, and regional gaps and needs in healthcare resources, services, and support. As the Project ECHO network in palliative care grows, so does the global stock of palliative care knowledge and best practices, as partners continue to teach and learn from one another in ever-widening communities of practice (Figure 2). ♦

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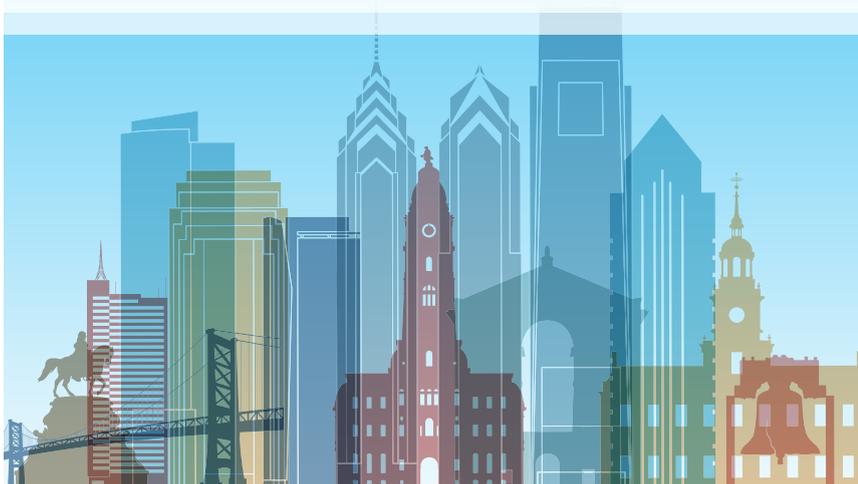
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Approved in frontline CLL with or without 17p deletion²



CLL
SLL

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

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)²
- CLL/SLL with 17p deletion²

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) 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, 19% to 29%), thrombocytopenia (range, 5% to 17%), and anemia (range, 0% to 9%) 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, 5% 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, 4% 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 drug, the patient should be apprised of the potential hazard to a fetus.

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 trial³

EXTENDED OVERALL SURVIVAL

IMBRUVICA® significantly extended OS vs chlorambucil²

Statistically significant reduction in risk of death²

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)

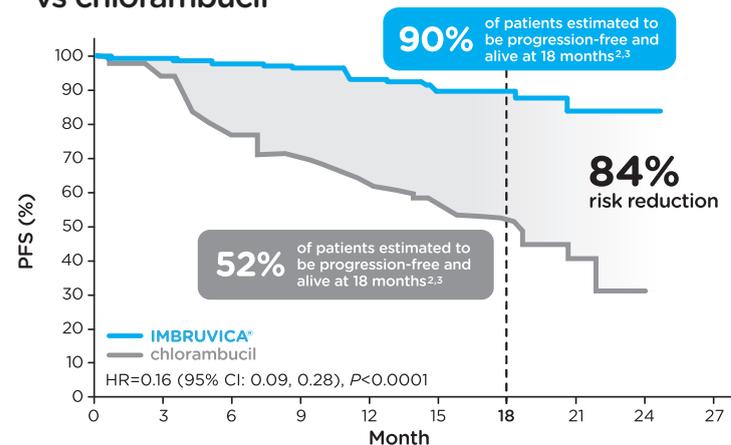
84% chlorambucil
(95% CI: 77, 90)

SECONDARY ENDPOINT: OS

- Median follow-up was 28 months²

PROLONGED PROGRESSION-FREE SURVIVAL

IMBRUVICA® significantly extended PFS vs chlorambucil^{2,3}



N at risk:

	0	3	6	9	12	15	18	21	24	27
IMB	136	133	130	126	122	98	66	21	2	0
CLB	133	121	95	85	74	49	34	10	0	0

PRIMARY ENDPOINT: PFS

- Median follow-up was 18 months⁵
- IMBRUVICA® median PFS not reached²
- Chlorambucil median PFS was 18.9 months (95% CI: 14.1, 22.0)²
- PFS was assessed by an IRC per revised IWCLL criteria³

Adverse reactions ≥20% across CLL/SLL registration studies²

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

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, and WM) were neutropenia[†] (64%), thrombocytopenia[†] (63%), diarrhea (43%), anemia[†] (41%), musculoskeletal pain (30%), rash (29%), nausea (29%), bruising (29%), fatigue (27%), hemorrhage (21%), and pyrexia (21%).

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

The most common Grade 3 or 4 non-hematologic adverse reactions (≥5%) in MCL patients were pneumonia (7%), abdominal pain (5%), atrial fibrillation (5%), diarrhea (5%), fatigue (5%), and skin infections (5%).

Approximately 6% (CLL/SLL), 14% (MCL), and 11% (WM) of patients had a dose reduction due to adverse reactions.

Approximately 4%-10% (CLL/SLL), 9% (MCL), and 6% (WM) of patients discontinued due to adverse reactions. Most frequent adverse reactions leading to discontinuation were pneumonia, hemorrhage, atrial fibrillation, rash, and neutropenia (1% each) in CLL/SLL patients and subdural hematoma (1.8%) in MCL patients.

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.

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IMBRUVICA® (ibrutinib) capsules, for oral use

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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 of clinical benefit in confirmatory trials [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*].

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) 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, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) 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, 5 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, 4 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 MCL, CLL/SLL or WM. 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

IMBRUVICA® (ibrutinib) capsules

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
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
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 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 system organ class 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 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.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients 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

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 3 (continued)

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
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 system organ class 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 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 system organ class 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: The data described below reflect exposure to IMBRUVICA in an open-label clinical trial that included 63 patients with previously treated WM.

The most commonly occurring adverse reactions in the WM trial (≥ 20%) were neutropenia, thrombocytopenia, diarrhea, rash, nausea, muscle spasms, and fatigue.

Six percent of patients receiving IMBRUVICA in the WM trial discontinued treatment due to adverse events. Adverse events leading to dose reduction occurred in 11% of patients.

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 the WM trial.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (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 system organ class 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 (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.

Additional Important Adverse Reactions: Diarrhea: Diarrhea of any grade occurred at a rate of 43% (range, 36% to 63%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 15%) 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 12 days (range, 0 to 627), of Grade 2 was 37 days (range, 1 to 667) and of Grade 3 was 71 days (range, 3 to 627). Of the patients who reported diarrhea, 83% had complete resolution, 1% had partial improvement and 16% 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 88 days (range, 1 to 414 days). Of the patients with visual disturbance, 64% had complete resolution and 36% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 281 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 (includes multiple terms)

Respiratory disorders: interstitial lung disease (includes multiple terms)

Metabolic and nutrition disorders: tumor lysis syndrome [see Warnings & Precautions]

Skin and subcutaneous tissue disorders: anaphylactic shock, angioedema, urticaria

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 sternbrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

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

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

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

Contraception:

Females: Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males: Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

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

Geriatric Use: Of the 839 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 21% were ≥ 75 years of age. No overall differences in effectiveness were observed between younger and older patients. Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA [see Clinical Studies (14.2) in Full Prescribing Information].

Hepatic Impairment: Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function.

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

Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with moderate or severe hepatic impairment (Child-Pugh class B and C) [see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information].

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

PATIENT COUNSELING INFORMATION

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

- Hemorrhage:** Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures [see Warnings and Precautions].
- Infections:** Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection [see Warnings and Precautions].
- Atrial fibrillation:** Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort [see Warnings and Precautions].
- Hypertension:** Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy [see Warnings and Precautions].
- Second primary malignancies:** Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas [see Warnings and Precautions].
- Tumor lysis syndrome:** Inform patients of the potential risk of tumor lysis syndrome and report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions].
- Embryo-fetal toxicity:** Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA [see Warnings and Precautions].
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day [see Dosage and Administration (2.1) in Full Prescribing Information].
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose [see Dosage and Administration (2.6) in Full Prescribing Information].
- Advise patients of the common side effects associated with IMBRUVICA [see Adverse Reactions]. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions].
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration.

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PAYER PERSPECTIVE

The Carrot or the Stick? Integrating Palliative Care Into Oncology Practice

Torrie K. Fields, MPH

continued from cover

that when integrated early in the treatment process, palliative care is associated with an increase in quality of life, satisfaction with care, an improvement in symptom burden for both patients and caregivers,¹⁻³ and longer survival.² While the evidence for palliative care has been compelling, the integration of palliative care into cancer care is moving slowly, requiring considerable changes in paradigm and ideology for oncologists as well as shifts in process flows for their practices. As financing for cancer care begins to shift from fee-for-service (FFS) to value-based payments, payers have an opportunity to incentivize and regulate services provided to patients and their families that can support oncology teams to provide high-quality care transitions for cancer patients in any stage of disease—from point of diagnosis, through treatment, and nearing end of life or survivorship.

Current State of Cancer Care

Economist Michael Porter defines value in healthcare as “patient health outcomes achieved per dollar spent,” emphasizing that the health outcomes achieved should focus on the patient’s preferences and defined measures for success, rather than strictly clinical effectiveness of treatment or survival rate.⁴ FFS cancer care does not factor in the quality of care provided and largely emphasizes impetus towards providing costlier and more aggressive services, thereby straining the healthcare system with the cost of experimental and targeted therapies and increasing the exposure of financial toxicity on patients and caregivers. Often, these treatments are in direct opposition to patient preferences.⁵ Even with health insurance, 10% of Medicare beneficiaries without supplemental insurance have been found to spend over 60% of their annual income on out-of-pocket expenses following cancer diagnosis.⁶ Twenty-five percent of participants in a Kaiser Family Foundation study reported using all or most of their savings dealing with cancer, while 33% of families reported a problem paying their cancer-care bills.⁷

Despite the variability in quality of care and financial impact on patients and caregivers, advances in treatment and precision medicine have increased the number of cancer survivors in the United States.⁸ With growing urgency to balance the delivery of high-quality cancer care with costs, stakeholders—including the Centers for Medicare & Medicaid Innovation (CMMI)—are developing new financial and clinical models that emphasize value.

Earlier Attempts at Practice Transformation

When moving from clinical-imputed value of treatment to the patient-perceived value of cancer care, it is imperative to include additional domains to determine the overall value of a test, procedure, or treatment. Suffering in cancer patients can be derived from multiple factors, including uncontrolled symptoms, inadequate psychosocial support, financial toxicity, inadequate understanding of prognosis or treatment options, disregard for patient preferences for treatment or setting, or even prolongation of the dying process in terminal cases. In 2012, in an effort to mitigate this, the American Society of Clinical Oncology (ASCO) and the American Board of Internal Medicine Foundation launched, as part of the Choosing Wisely campaign, the top 5 list of tests and procedures in oncology care that should be questioned due to

their failure to add further clinical value to the course of cancer treatment for a patient. The list was compiled with input from more than 200 oncologists and was used to promote communication among oncologists about best practices in delivering higher-value care. With 2 procedures highlighting improper management of pain and symptoms under Choosing Wisely, one recommendation from ASCO was earlier integration of palliative care into the treatment plan for those patients with advanced cancer.⁹

In a retrospective review of this list and of adherence to the Choosing Wisely recommendations, it was found that not only was adherence highly variable, but that aggressive care did not decrease following implementation of these recommendations. Overall adherence to these measures ranged from 53% to 78%, with adherence being poorest for patients diagnosed with advanced cancers. With the palliative care measure in particular, adherence ranged from 60% at 90 days from the date of death to 89% at 14 days from the date of death.¹⁰ These results indicate that early integration of palliative care into cancer care is largely nonexistent, with referrals to hospice or palliative care coming consistently only in the last 2 weeks of life. This late-stage integration does not allow a patient or caregiver to experience the full effect of palliative care’s ability to alleviate suffering throughout the care continuum, and it suggests that aggressive, often unwanted, therapy is occurring until the patient is very near death.

Often overlooked as a hurdle to the integration of palliative care into cancer care is that graduate medical education includes only limited training in communication skills and care coordination. This training often does not continue once a new doctor selects a specialty, such as oncology. A considerable amount of evidence suggests that communication skills training in oncology practice has the ability to help healthcare professionals demonstrate feelings of empathy, address stressful and difficult situations, improve care transitions, and improve the quality of medical care and satisfaction for patients and families.¹¹ However, the receipt of such training is dependent upon the interest and initial comfort level of an oncologist to pursue and continue such training on their own time, as part of continuing medical education. This results in a workforce that is highly variable in its ability to communicate with patients and families about prognosis, treatment goals, or the clinical value of cancer treatment being administered.

Practice transformation is also limited by the variability in quantifiable process and outcome measures being used by all value-based purchasing programs, including those for cancer care. In a review of 129 publicly available value-based purchasing programs, the Rand Institute found that there is a high degree of variability in measures chosen for clinical appropriateness of care, patient preferences and satisfaction, and care centered on patient functional status.¹² The high level of experimentation in the area of value-based purchasing and bundled payments has generated mixed results on the effectiveness of these types of programs, further increasing the hesitance of providers to transform their practices to achieve »

blue  of california

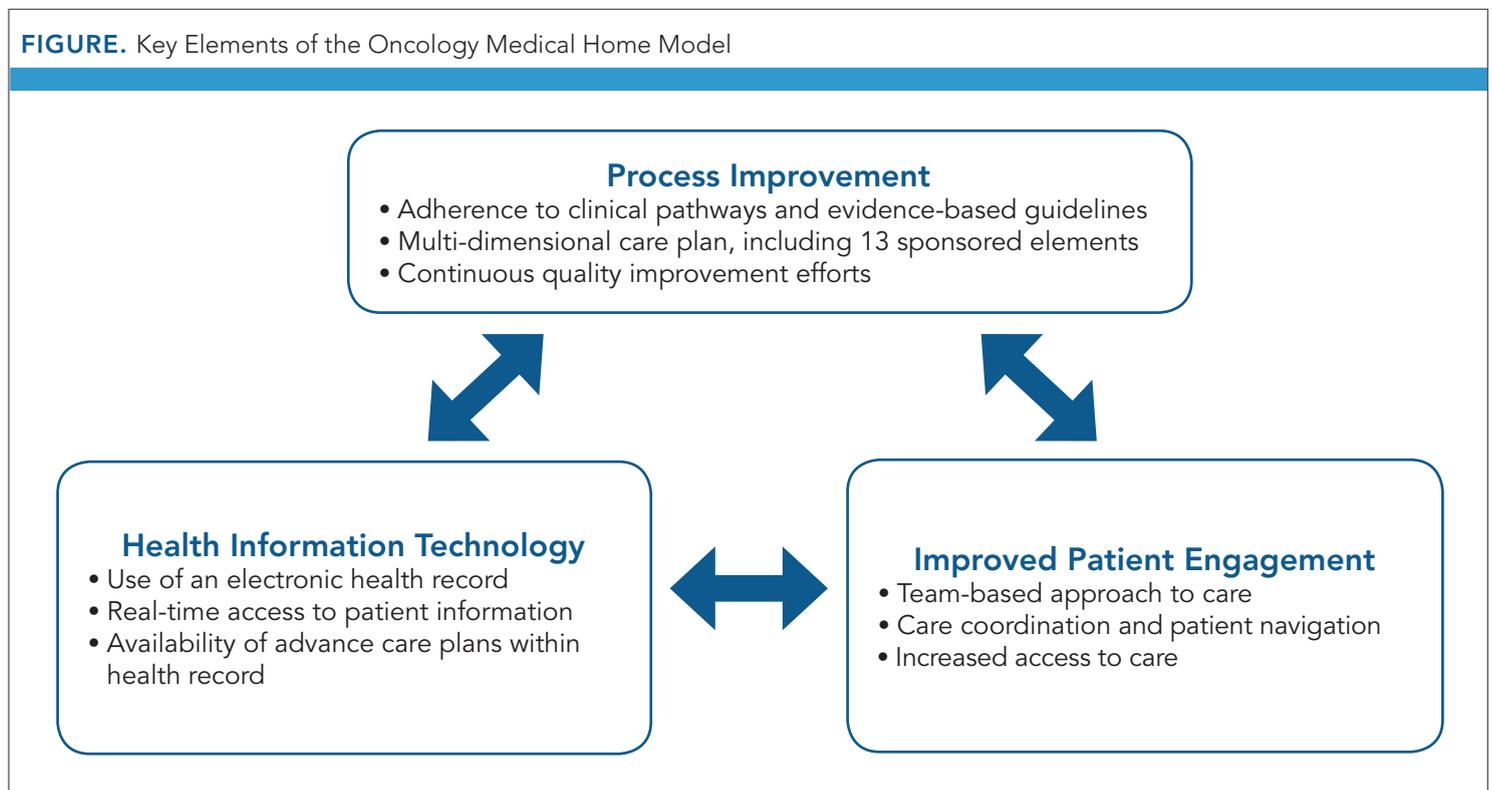


FIELDS

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IN ADDITION TO BUNDLED PAYMENT REIMBURSEMENT, PAYERS ARE EXPERIMENTING WITH ADDITIONAL INCENTIVES AND REGULATORY CRITERIA TO BETTER INTEGRATE PALLIATIVE CARE INTO ONCOLOGY, BEGINNING AT THE POINT OF DIAGNOSIS.

FIGURE. Key Elements of the Oncology Medical Home Model



stipulated targets. Among those successful programs, the elements determined to improve clinical outcomes included considerable financial incentives and alignment on quality, utilization, and performance targets, as well as provider training, engagement, and support for quality improvement initiatives and reporting requirements in the electronic health record (EHR).¹²

Blending Incentives and Support to Integrate Palliative Care Into Oncology Practice

The practice of integrating palliative care into oncology practice has been gaining considerable traction with the implementation of bundled payment programs for oncology and the introduction of the Oncology Medical Home (OMH) model.¹³ Most notable is the implementation of the Oncology Care Model (OCM) by CMMI, a demonstration project focused on improving the value of cancer care for Medicare beneficiaries. OCM and multiple other oncology bundled payment models being piloted throughout the country focus on the use of incentives and reporting criteria to align patients undergoing active cancer treatment to evidence-based pathways and additional support for care coordination. Performance is measured using cost, quality, and patient satisfaction targets.

Bundled payment programs for oncology, including OCM and OMH, require practice transformation (**Figure**).^{14,15} While these requirements may be possible to achieve by a larger oncology practice with considerable operational infrastructure and support, independent oncologists and smaller practices may have more difficulty implementing change. Because palliative care teams are focused on providing a team-based approach to care, care coordination, and a multi-dimensional care plan documenting treatment preferences, the integration of palliative care or a partnership with a palliative care team can be used to facilitate practice transformation and provide a higher degree of patient-centered care.¹⁶

In addition to bundled payment reimbursement for providing oncology care, payers are experimenting with additional incentives and regulatory criteria to better integrate palliative care into oncology beginning at point of diagnosis. Incentives and regulation range from more standard approaches under value-based purchasing to those that are more innovative in nature, all with

considerations that must be weighed prior to implementation.

One standard approach to incentivizing the integration of palliative care into oncology practice is the additional ability for oncology practices to achieve a higher percentage of shared savings or provider performance bonuses based on specific process and quality targets, focusing on this integration. For example, a proposed process measure by which to increase an incentive payout would be the documentation of a medical surrogate for all patients diagnosed with cancer or the documentation of Eastern Cooperative Oncology Group status, both of which are indicators of, or drivers for, early palliative care intervention. An example of a quality outcome measure would be the hospice referral rate or median length of stay (LOS) on hospice for patients with metastatic cancer. By incentivizing the median LOS on hospice, oncologists would need to engage the patient early and often regarding treatment preferences, including preferred place of death. Payers and providers alike must be cautious in measure selection, as not all patients will prefer hospice or wish to die at home, and this must be taken into account in reporting and calculation of incentive payouts.

Other approaches that have been proposed include additional reimbursement for palliative care, including bundled payments specifically for palliative care services that would align but not compete with the bundled payment for oncology. This approach allows for the oncologist and patient to receive an extra layer of support that focuses on pain and symptom management but does not compete with the payment made to the oncologist for care being provided. Models that embed or integrate a palliative care practitioner or team are most successful when incentives and outcomes are aligned and work together to minimize the impact of multiple providers and appointments on the patient and family undergoing treatment. Continuity and coordination of care should be at the center of treatment, with both the palliative care and oncology team remaining involved throughout the course of the disease, including through death. Some proposed payment methods reinforce this idea by continuing bundled payment reimbursement for the oncologist as the patient transitions to hospice. However, this is not ideal in practice transformation, as the goal of integrating palliative care into oncology practice is to ensure

that all clinicians on the patient care team are operating at the top of their license. Continuing to have active management of the patient by an oncologist while the patient elects hospice does not encourage the best use of resources, but it is highly encouraged that the oncologist continues as part of the care team, monitoring and engaging with the patient even after hospice election.

As evidenced from the mixed results on the impact of value-based purchasing on clinical outcomes, financiers and regulators of healthcare cannot depend solely on incentives, financial or otherwise, to transform clinical practice. To ensure that patients and families can receive high-quality care while being protected from unwanted medical treatment and financial toxicity, safeguards must be put in place to assist clinicians in making evidence-based decisions that align with the goals and preferences of patients with cancer and their caregivers. A majority of regulatory approaches proposed by payers to maintain value in cancer care and reduce the variability of care that is delivered are focused on the alignment of treatment protocols with evidence-based pathways as designated by the National Comprehensive Cancer Network's Clinical Practice Guidelines. However, adherence to these guidelines does not outwardly encourage integration of palliative care into cancer care and often restricts providers from feeling like they can continue practicing the art of medicine.

One way to support providers in making decisions considering multiple domains of the patient's care is through early and regular integration of palliative care into clinical treatment. Payers implementing an FFS or bundled payment model for oncology treatment often have prior authorization requirements. Integrating palliative care consultation requirement prior to authorization of any form of cancer treatment can ensure that the patient and caregiver remain at the center of the treatment plan, that they understand the prognosis and treatment options, and that they have documented goals of care. This is evidenced by studies showing that just the first palliative care consultation, in either an inpatient or outpatient setting, resulted in patients reporting an improved quality of life, improved satisfaction with the treatment plan and provider, improvement in physical and psychological symptoms, and reduction in financial toxicity.^{3,17} In addition, payers can require shared decision-making documentation and ongoing documentation of palliative care consultations at different points during treatment, including when a change is made in a treatment plan, upon beginning subsequent treatment, or following a cancer-related inpatient admission.

Other regulations that will further reinforce the integration of palliative care into oncology practice include the requirement for additional documentation in the patient's EHR and the requirement of a care coordinator responsible for treatment team communication and care transitions. Both these criteria are requirements under the OCM and under many other OMH models being piloted. Areas necessary to be captured by the EHR include documentation of: the patient's medical surrogate; the goals of care using a standardized assessment; and advance care planning documents, including an advanced directive and a Physician Order for Life Sustaining Treatment, where appropriate. Documentation of patient preferences and goals of care, as well as the implementation of a team-based approach to cancer care, become imperative with the intense needs of patients and caregivers facing a cancer diagnosis and the increasing complexity and cost of cancer care.

Conclusion

Undergoing practice transformation, including the integration of palliative care into oncology practice, is no small feat. It takes more than financial incentives and outcomes measures, including increased provider education, training, and support, for change to

occur and be sustained over time. While regulations for oncology practice increase in an attempt to bend the cost curve and improve quality, palliative care can provide an extra layer of support for the patient and the provider alike, injecting the art of practice that keeps the patient at the center of care. ♦

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PHARMACIST'S ROLE

Transitions of Care in Patients With Cancer

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

continued from cover



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In 2013, the cost of 500,000 readmissions was \$7 billion, and the most common disease states contributing to this cost were acute myocardial infarction (AMI), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and pneumonia (PNA).²

Several factors, including older age, polypharmacy, comorbidities, functional impairment, and the lack of ideally structured transitions of care (TOC) programs to provide safe and effective care, may increase risk of readmissions and influence post discharge AEs.³ In efforts to reduce cost of readmissions, the Affordable Care Act introduced the Hospital Readmissions Reduction Program in 2010. This program allowed for decreases in Medicare reimbursement for acute care hospitals, except cancer and critical access hospitals, that did not meet targets for hospital readmissions within 30 days. The program focused on high-volume disease states that accounted for a large percentage of readmissions such as AMI, CHF, COPD, PNA, and vascular procedures.⁴

According to the National Cancer Institute (NCI), the cost of cancer care was estimated to be \$125 billion in 2010 and could increase to \$156 billion in 2020.⁵ NCI estimates that the number of new cancer cases in the United States will increase to 22 million within the next 20 years, with about 1.7 million patients newly diagnosed in 2017.^{5,6} However, survivorship of cancer patients has increased due to new advances in treatment.⁶ Over the last 15 years, the use of oral chemotherapy has nearly doubled⁷; still, the availability of these agents has, in part, transferred the responsibility of proper storage and administration to the patient, leading to difficulties with adherence and safety.⁸⁻¹⁰

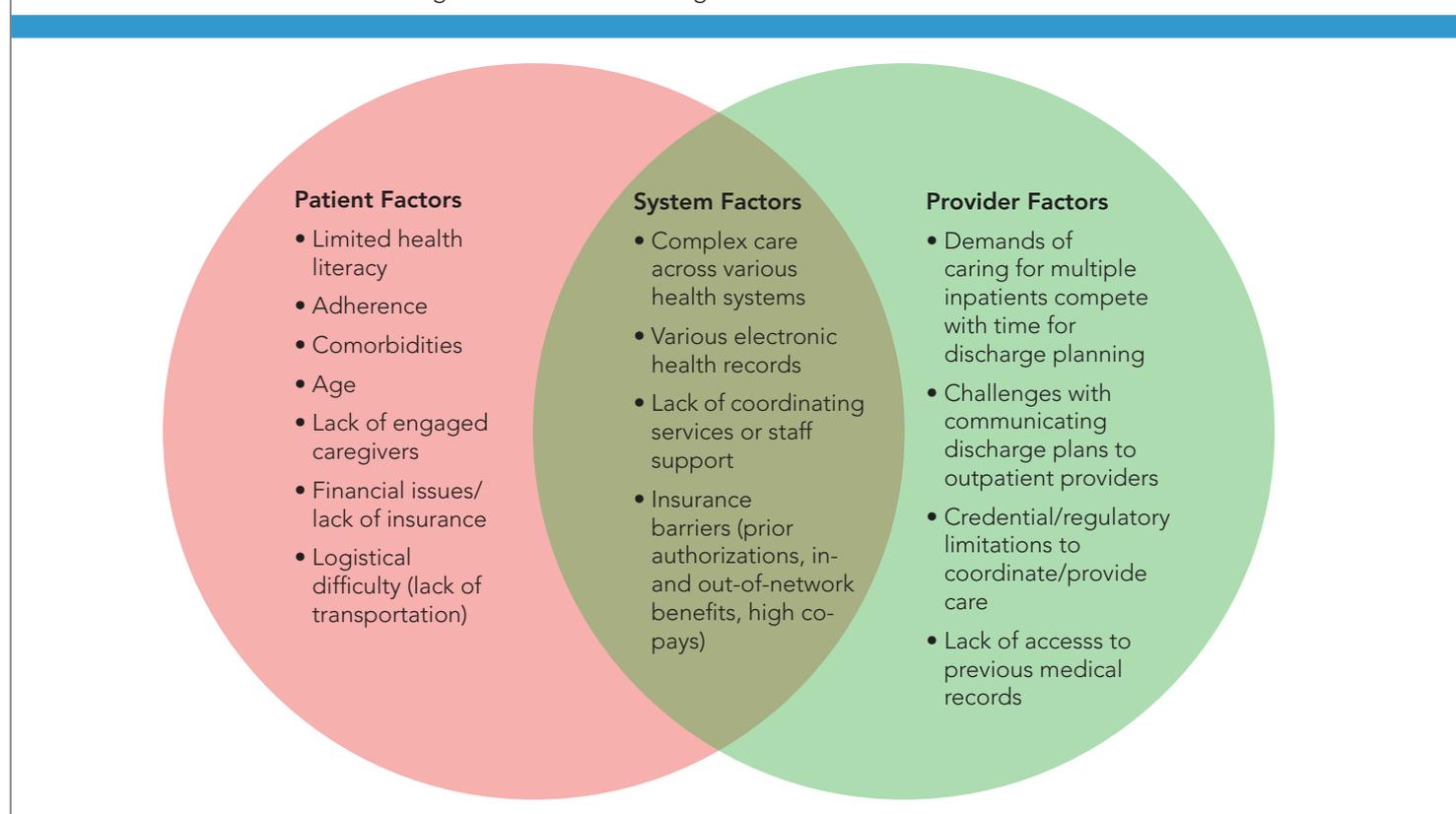
Administration of antineoplastic medications in the inpatient and outpatient settings is complex, with variations in length of doses within a cycle. In addition to the cancer treatment, patients may receive antimicrobials to prevent infections; granulocyte-colony stimulating factors (G-CSFs) to prevent neutropenia; and other medications to help prevent and/or treat nausea, pain, diarrhea, constipation, and/or thromboembolism. Additionally, patients are living longer and inherently have more chronic comorbidities that necessitate medications taken concurrently with the cancer treatment. This scenario is a prime setup for potential errors for patients managing these medications at home.

Although cancer institutions are exempt from the current measures, it is likely that in the future, these institutions will be held accountable for readmissions and other major patient outcomes, as acute care hospitals currently are. Cancer centers need to adopt TOC processes that coordinate care for both complex cancer treatment and the patients' associated comorbidities to ensure optimal care for this high-risk patient population.

Transitions of Care Models

Currently, no consensus exists on a gold-standard TOC program, but some essential components include medication reconciliation, structured discharge communication and facilitation, patient education, and timely post discharge follow-up. There are overlapping TOC challenges for patients, providers, and the healthcare system (Figure).

FIGURE. Transitions of Care Challenges in Patients Receiving Cancer Treatment



Medication Reconciliation

The Joint Commission has recognized medication reconciliation as a national patient safety goal to enhance continuity of care in medication management.¹¹ Obtaining an accurate medication history is often challenging in the inpatient setting, and multiple sources of information are often needed to achieve this goal. Pharmacy technicians and pharmacy learners (eg, residents and students) can assist pharmacists in obtaining information from the patient, caretakers, medication lists within the electronic health record (EHR), outside pharmacies, and/or outpatient provider offices.¹² Key components of a medication history are listed in **Table 1**.¹³ Any other medication-related information that may assist the inpatient team in making the best decisions for the patient's current treatment plan should also be collected. After obtaining a complete medication history, a pharmacist should reconcile this information with inpatient medications to identify any discrepancies or omissions. The pharmacist will then discuss this information with the care team and facilitate making appropriate changes to active inpatient orders. This practice has been shown to prevent medication errors and reduce AEs.¹²

Medication Education and Postdischarge Follow-Up

Patients' understanding of medication changes made during their hospitalization, and of their discharge medication regimens, may be hampered by complex treatment, limited health literacy, and/or language barriers.¹⁴ To overcome these barriers, appropriate medication education and structured discharge communication must be provided to clearly articulate both treatment and overall discharge instructions. Cancer care team members, including nurses and pharmacists, can help educate patients about their medications by using teach-back method to confirm understanding.¹⁵ Pharmacists can be particularly helpful in targeting patients being discharged on new high-risk medications and/or those patients whose new medication regimen has undergone many changes compared with their prior-to-admission home medications. Initiating the education process as soon as the discharge regimen is confirmed is important because of the significant information burden that the patient faces on the day of discharge. Chemotherapy calendars and medication sheets, including a medication schedule, are helpful tools to help patients recall detailed instructions. Some institutions have implemented bedside discharge medication delivery to:^{16,17}

- Increase patients' access to discharge medications
- Increase patient convenience, by avoiding a retail pharmacy visit post discharge for medication pick-up
- Enhance medication adherence.

It is essential to have postdischarge communication, via face-to-face appointments or phone follow-up, to ensure a safe transition from hospital to home.^{18,19} Dickinson and colleagues conducted a systematic review of studies using various technologies such as telephone, clinical decision support, automated voice response symptom reporting, or smartphone applications to follow up with patients after initial cancer treatment.¹⁸ Based on the results, investigators concluded that these technology-based interventions did not compromise patient satisfaction or safety when they measured symptoms, health-related quality of life, or psychological distress.

Transitions of Care Initiatives

Although cancer centers around the country have been providing TOC services for several decades through pharmacists, nurses, and/or physicians,²⁰ they have not formally implemented TOC programs as quickly as other acute care centers. One reason for this is that a universal approach would not work for cancer centers, because the

TABLE 1. Components of a Medication History¹³

Medications (start and stop date, dose, route, and frequency)	Nonprescription medications Prescription medications (duration of therapy, missed doses, quantify as needed medication use, and last dose taken) Antineoplastic medications/regimen (date of last dose of each drug, day of cycle, duration of cycle)
Allergies and intolerance	Medication allergies Food allergies Intolerances to medications Adverse drug reactions (symptoms, severity, and how long ago) Enzyme deficiencies (eg, glucose-6-phosphate dehydrogenase)
Complementary and alternative medicines	Vitamins Herbal/natural products Dietary supplements
Preferred pharmacy	
Pregnancy status if applicable	
Medication cost, co-pay information, and insurance barriers	
Adherence challenges	

transitional care needs of these patients vary depending on the type of cancer. For example, adaptations in chemotherapy calendars, supportive care medications, and drug monitoring will be much different for a patient who has pancreatic cancer versus a patient who underwent a stem cell transplantation. However, to address the needs of the dynamic healthcare landscape, cancer centers are adapting principles of TOC similar to those at acute care institutions.

Pharmacists, as members of the healthcare team, play a major role in improving health outcomes, quality, and safety.²¹ Expanding their role in TOC programs has the potential for a large economic impact as it relates to the pharmacists' ability to decrease preventable AEs and subsequent readmissions. The Care Transitions trial provided needed resources and a nurse "transition coach" to patients older than 65 years of age after discharge and saw a decline in readmissions.²² Institutions have developed a variety of models that include pharmacists, pharmacy technicians, nurses, and providers, as well as combinations of any of the aforementioned healthcare team members. **Table 2** describes the potential role of TOC pharmacy members.

Several other TOC programs have been described in the literature. Project RED (Reengineered Hospital Discharge Program) utilized nurses to help reconcile medications, educate, and coordinate outpatient appointments while clinical pharmacists called patients 2 to 4 days post discharge.²³ In this study, which took place at an academic medical center located in an urban area, investigators found a lower hospital readmission rate for patients with these comprehensive interventions. Project BOOST (Better Outcomes by Optimizing Safe Transitions) implemented comprehensive TOC programs at 6 hospitals in Illinois.²⁴ The implementation of physician mentors, who provided training and guidance to physicians, in Project BOOST demonstrated a reduction in hospital admissions by intervening with specific high-risk patients and facilitating communication and coordination between outpatient providers and patients.

In 2013, the American Society of Health-System Pharmacists (ASHP) and the American Pharmacists Association (APhA) collaboratively published the ASHP-APhA Medication Management in Care Transitions Best Practices. This guidance was published after reviewing more than 80 institutions' TOC programs, and served to highlight 8 TOC models that best demonstrate the integration of pharmacists in care transition teams.²⁵ »

OBTAINING AN ACCURATE MEDICATION HISTORY IS OFTEN CHALLENGING IN THE INPATIENT SETTING, AND MULTIPLE SOURCES OF INFORMATION MAY BE NEEDED TO ACHIEVE THIS GOAL.

TABLE 2. Comprehensive Transitions of Care Model: Team Member Roles

	Pharmacy Technicians ^a	Pharmacy Learners ^{a,b}	Clinical Pharmacy Specialists ^c	Integrated Clinical Pharmacists ^d	Inpatient Pharmacists ^e	Outpatient/Retail Pharmacists ^f
Medication history						
Medication reconciliation						
Patient education						
Discharge medication coordination and delivery						
Postdischarge phone or in-person follow-up						

^aPerform activities under the supervision/review of a pharmacist.
^bPharmacy learners: pharmacy students and pharmacy residents.
^cRounding pharmacist with no order verification role (clinical duties only).
^dBoth rounding and order verification role (clinical and operational duties).
^eOrder verification role (operational duties only).
^fProvide education for discharge medications if delivery program is available.

They chose the programs based on the impact of the model on patient care, pharmacists' involvement in the transition process from hospital to home settings, and how adaptable the program was perceived to be in terms of implementation by other health systems. The 8 programs were implemented at²⁵:

- Einstein Healthcare Network (Philadelphia, Pennsylvania)
- Froedtert Hospital (Milwaukee, Wisconsin)
- Hennepin County Medical Center (Minneapolis, Minnesota)
- Johns Hopkins Medicine (Baltimore, Maryland)
- Mission Hospitals (Asheville, North Carolina)
- Sharp HealthCare (San Diego, California)
- University of Pittsburgh School of Pharmacy and University of Pittsburgh Medical Center (Pittsburgh, Pennsylvania)
- University of Utah Hospitals and Clinics (Salt Lake City, Utah).

In addition to the best practices above, numerous studies show positive impact on patient outcomes when pharmacists are key participants in various TOC models.^{16,26-28}

While there is a demonstrated need for pharmacist involvement in these services, institutions are often expected to provide these services in a resource-neutral fashion. Challenges arise when departments of pharmacy are faced with a need to deploy more of their staff to gather medication histories, educate patients, and complete post discharge follow-up while maintaining all existing operational and clinical services. One academic medical center approached this problem by taking an inventory of all responsibilities of current staff (order verification, clinical service provision, triage of calls to the pharmacy, missing medications, etc) and reallocating responsibilities. This resulted in a decrease in order-verification responsibilities for a number of pharmacists, allowing them more time to interact directly with patients without compromising overall workflow and safety from an order verification standpoint. Since these pharmacists were now spending more time directly on the units, they were able to

take on additional responsibilities in triaging requests of nursing staff and providers, which allowed for an increase in order-verification responsibilities for some pharmacists due to assistance with those tasks.²⁹

Meanwhile, development of formal oncology-specific TOC programs are underway. For their oncology patients admitted to the palliative medicine and solid tumor oncology inpatient services, the Cleveland Clinic implemented a TOC program with the following components:³⁰

1. Provider education
2. Post discharge nursing phone calls within 48 hours
3. Post discharge provider follow-up appointments within 5 business days.

Nurses provided symptom management, education, medication review, and a follow-up appointment reminder. The overall program helped reduce readmissions by 4.5% and provided \$1.04 million in annual cost savings.³⁰ With support from the ASHP Pharmacy Practice Advancement Initiative grant, the University of Texas at MD Anderson Cancer Center (UT MDACC) started a TOC pilot program to include medication reconciliation, education, discharge medication deliveries, and a 72-hour postdischarge phone follow-up.^{31,32} The team, consisting of pharmacy trainees, inpatient pharmacists, outpatient pharmacists, and clinical pharmacists, collaborates closely with internal medicine inpatient providers and coordinates care with outpatient providers to ensure safe and effective patient care. The outcomes for the TOC pilot, which is currently ongoing, are 30-day readmissions and adherence rate.

Even though the data have not been analyzed, it is evident that this program will have a positive impact on safe and effective patient care delivery. Many medication-related AEs have been prevented or caught during medication reconciliation, discharge education, and phone follow-up. For example, the TOC team caught the absence of numerous critical medications that had been accidentally omitted from patients' inpatient medication list, such as antiarrhythmics, pain medications, antidepressants, and antihypertensives. The TOC pharmacists have also recommended discontinuation of high-alert medications that were deemed inappropriate to restart in the hospital due to the patient's condition, such as anticoagulants in a patient with a concern for a bleed. Another example is that upon phone follow-up, TOC pharmacists were able to help reschedule a missed outpatient antibiotic infusion appointment, which likely prevented a readmission.

Some challenges for the TOC program include limited resources and time constraints, as the pharmacists must fulfill their daily responsibilities in addition to TOC activities. There are scheduling challenges with staff pharmacists, which limits continuity of TOC activities when multiple staff pharmacists cover a unit throughout the week. In addition, there is rapid turnover of TOC team members, mostly pharmacy students who are doing their rotations for a finite period. This turnover increases the workload on TOC pharmacists to continuously train new TOC team members to perform medication history and reconciliation. Utilization of pharmacy technicians or pharmacy interns would be a potential solution.

To overcome some of the challenges mentioned above, UT MDACC is implementing a new pharmacy practice model in

A PRIMARY CANCER TREATMENT TEAM SHOULD BE ESTABLISHED TO ENSURE CARE COORDINATION, WITH THE PHARMACISTS INVOLVED IN ALL PHARMACOTHERAPY ASPECTS THROUGHOUT THE PATIENT'S TRANSITIONS WITHIN THE HEALTHCARE SYSTEM.

addition to the TOC program; it will have integrated clinical pharmacists (ICPs) with operational and clinical responsibilities, such as order verification, triaging nursing/provider questions, anticoagulation monitoring, renal monitoring, and TOC activities. The goal for these ICPs is to provide consistent continuity of care on the patient unit that they are following.

Overall, current research, such as the Care Transitions trial, Project RED, Project BOOST, and ASHP-APhA Medication Management in Care Transitions Best Practices, suggests that having a comprehensive TOC program is more effective in lowering readmissions than is targeting individual components.²²⁻²⁵ The pharmacist should play an active role on an interdisciplinary team to provide safe and effective care to patients.

Models of Cancer Care Delivery

Cancer treatments are administered in a variety of settings, ranging from a small private practice to a large academic comprehensive cancer treatment center. Clinical outcomes may differ for certain disease states based on setting; for example, patients with a rare hematologic malignancy, multiple myeloma, who were treated at a high-volume center were found to have higher overall survival to those treated in community settings.³³ The volume-outcome relationship is well known for surgical management of solid cancers.³⁴ Some patients may not have access to a high-volume cancer treatment center given their geographical location, insurance network, or financial feasibility. Co-management is a potential solution, in which the patient receives treatment recommendations from a higher-volume center but visits a local physician to have the treatment plan implemented.³³ Whether cancer care is delivered in a small community hospital or a large academic medical center, a multidisciplinary team that includes a hematologist/oncologist, surgical oncologist, radiologist, palliative care providers, midlevel providers, pharmacists, social workers, case managers, and spiritual care providers is essential to meet patients' needs.^{35,36}

Of the total 69 NCI-designated cancer centers, 47 are comprehensive cancer centers that perform laboratory, clinical, behavioral, and population-based research. Fifteen of the 69 cancer centers perform basic, population sciences, and clinical research.³⁷ Many additional academic medical centers are not NCI-designated. Regardless of the shortfalls of respective models, cancer treatment teams need to identify the shortfalls of their models and adapt their approach to account for the diversity in practice settings where cancer care is delivered, although it may be challenging to coordinate the various fragmented services to ensure provision of comprehensive care. A primary cancer treatment team should be established to ensure care coordination, with the pharmacists involved in all pharmacotherapy aspects throughout the patient's transitions within the healthcare system.

Cancer Treatment Challenges

Antineoplastic medications can be administered in the outpatient or inpatient setting depending on the type of regimen, insurance coverage, and center where the drug is being administered. Starting cancer treatment requires careful coordination with the patient's insurance carrier to obtain pre-approval for high-cost antineoplastic medications, and G-CSF if clinically indicated. Additionally, care teams can help patients enroll in patient financial assistance programs to help cover high-cost medications.³⁸ Some chemotherapy regimens that require an infusion pump, such as continuous-infusion fluorouracil, may require working with outside infusion companies; patient education must also be provided. Furthermore, long commutes to clinics for patients undergoing cancer treatment can be strenuous on patients and caregivers. Coordinating patients' schedules to combine appointments can minimize trips and decrease the patient's stress.

Cancer treatments range from simple once-a-day oral medications to multiple inpatient and outpatient infusion treatments with variations in "on" and "off" periods, further complicating the administration of cancer care. Regimens of such medications as hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone require an initial inpatient infusions followed by outpatient infusions.³⁹ Patients need to be informed of complex drug dosing frequencies such as weeks off treatment, as with regorafenib or dexamethasone pulses to prevent overdoses.^{39,40} Certain supportive-care medications like azole antifungals may need to be taken around the time of each chemotherapy session to prevent drug interactions, which adds to the complexity of the treatment.

Managing Care Transitions During Cancer Treatment

Managing complications of cancer treatment may require hospital admission and holding treatment. EHRs need to have the capability to put treatment plans on hold to prevent the administration of chemotherapy and biotherapy during the period when toxicities are being managed. Patients may need to continue intravenous antibiotics in the outpatient setting, requiring careful coordination with the case manager to set up home infusion services. Some large institutions have the ability to administer intravenous antibiotics, intravenous fluids, blood products, or G-CSF in the outpatient setting through an infusion center. In addition to medications, patients may have other needs such as setting up home oxygen, outpatient physical/occupational therapy, medical equipment, and home health services. Certain infusional chemotherapies, such as continuous infusion doxorubicin, require central line access; in such cases, patients must be provided with line care supplies and trained to care for their own lines.

Depending on the chemotherapy regimen, patients may need to have laboratory blood monitoring in the outpatient setting, in time patterns ranging from once a cycle to several times a week. Communication is essential when multiple physicians are involved in the management of a patient. Fortunately, EHRs are making those transitions easier. However, providers must still communicate among one another about a co-managed patient's cycles of chemotherapy, laboratory values, and changes in condition between cycles. These communications can be meaningfully achieved through physical or electronic letters sent to the co-managing physician. Sample orders including chemotherapy and biotherapy as well as supportive care medications may be provided for physicians taking over care for subsequent cycles. Pharmacists at large cancer centers with experience with the regimens can collaborate with smaller centers to ensure optimal delivery of the regimens. Patients may need to go to skilled nursing, long-term acute care, rehabilitation, or hospice facilities. It is important for care teams to provide clear medication, laboratory, and monitoring support to these facilities, as they may not be accustomed to monitoring these types of patients.

Conclusions

Cancer care is complex and requires an interdisciplinary approach with careful coordination of many specialties. While cancer treatment providers and supportive professionals have been providing these services, they are adapting care delivery to enhance quality and reduce cost, based on incentives provided by health plans. TOC models are being evaluated to enhance the transitions of patients undergoing cancer care. Coordination by the primary treatment team and thorough medication reconciliation and education provided by pharmacists, in conjunction with appropriate follow-up, is essential to ensure optimal outcomes and minimize AEs. ♦

PROVIDERS ARE ADAPTING CARE DELIVERY TO ENHANCE QUALITY AND REDUCE COST, BASED ON INCENTIVES PROVIDED BY HEALTH PLANS.

ADDITIONAL RESOURCES



Community pharmacists can have a significant impact on reducing hospital readmissions.

Here's how they can do it: pharmacytimes.com/link/160.

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DISCLOSURES

None

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