SPECIAL ISSUE: TECHNOLOGY IN CANCER CARE

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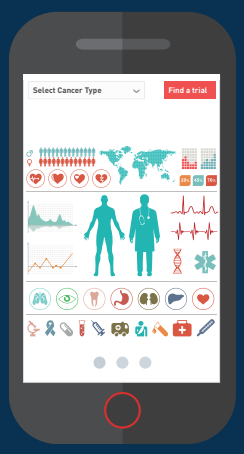
ALSO IN THIS ISSUE



SP548

Virtual trial assistants, like the one created by Clara Health, help keep patients engaged in the trial enrollment process.

TARGETING RISK, COST

Authors from Integra Connect write how oncologists can use technology to reduce costs and improve outcomes in 2 ways: identifying their highest-risk patients and delivering programs to prevent low- and moderate-risk patients from becoming high risk, SP514.

PATIENTS AT THE CENTER

At the National Comprehensive Cancer Network (NCCN) Oncology Policy Summit, held September 25 in Washington, DC, Ronald Walters, MD, MBA, MHA, MS, of Texas MD Anderson Cancer Center told listeners about a recent shift in quality measures. The change has moved providers from the center and put patients first. But, Walters asked, "Why aren't these measurements a key part of the health system yet?" For coverage from the NCCN conference, see SP517, SP522.

EXPERIENCE COUNTS

At the Community Oncology Alliance (COA) Payer Exchange Summit on Oncology Payment Reform, held October 23-24 in Tysons Corner, Virginia, Basit Chaudhry, MD, PhD, and Celeste Roschuni, PhD, of Tuple Health explained the categories of users of the CMS Oncology Care Model (OCM), and said prior use of an alternative payment model matters more than practice size. For coverage of the COA meeting and more on the OCM, see SP523, SP525, SP530.

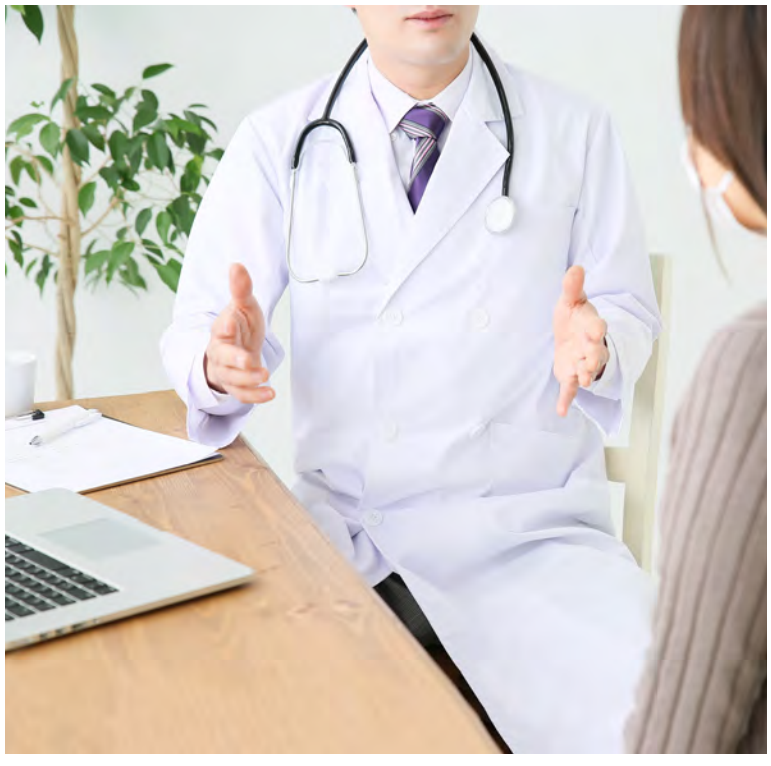
PHYSICIAN-PATIENT INTERACTION

EHR Documentation and the Patient–Physician Visit

Sheree Starrett, MD, MS

IN 1999 AND 2001, the Institute of Medicine (IOM) issued reports that galvanized the medical community about healthcare quality. The 1999 report, *To Err Is Human: Building a Safer Health System* highlighted the negative role that medical errors play in healthcare quality.[1] Extrapolating from reviews of adverse events in Colorado, Utah, and New York, the authors concluded that between 44,000 and 88,000 Americans die annually as a result of medical errors; the cost in dollars was likewise very high. The authors reported that "total national costs—lost income, lost household production, disability, and healthcare costs—were estimated to be between $17 billion and $29 billion, of which health care costs represented over one-half."[1]

Stressing the need to adopt a culture of safety within the American healthcare system to improve its quality, the authors noted that blaming individuals for errors was not useful—the focus should be "on preventing future errors by designing safety into the system." The report further emphasized the importance of information technology and the need for computerized patient records, which would benefit patient care.



Electronic media should enhance patient-centered care, in tandem with a trusting physician-patient relationship.

CONTINUED ON SP539

TRIAL ENROLLMENT

How Technology, Social Media Are Changing the Way Clinical Trials Connect With Patients

Mary Caffrey

THE INSPIRATION FOR CLARA HEALTH came when co-founder Sol Chen was walking across campus at Brown University and saw a paper flier seeking patients for a breast cancer drug trial. Surely, she thought, there had to be a better way to find people who needed life-saving medications.[1]

For Seeker Health's Sandra Shpilberg, MBA, the moment of clarity came when her former company, Nora Therapeutics, was struggling to find women to test a potential treatment for recurrent miscarriage.[2] Instead of waiting for women to appear in clinics, Shpilberg set out to find them online—with ads that targeted women based on Facebook groups they'd joined or other common interests.

"That worked very well," Shpilberg said in an interview with *Evidence-Based Oncology*™ (*EBO*™). "So, I decided to start a company to help many other sponsors."

Companies like Clara Health and Seeker Health are using digital tools, including social media, to rewrite

CONTINUED ON SP548

PATIENT-REPORTED OUTCOMES

Q&A With Dr Thomas LeBlanc: The Value of ePROs in Oncology

Surabhi Dangi-Garimella, PhD

PATIENT-REPORTED OUTCOMES (PROs) are finding a significant place in healthcare quality metrics, and PROs are sometimes thought to be more reliable than clinician-reported data. The challenge continues to be adopting service workflows to collect this information from patients, and electronic PROs (ePROs) have definitely enhanced this process.

Evidence-Based Oncology™ (*EBO*™) spoke with Thomas W. LeBlanc, MD, medical oncologist, Duke University School of Medicine, Durham, North Carolina, about the real-world influence of PROs.

CONTINUED ON SP550

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- As monotherapy for the treatment of adult patients with HR+, HER2– advanced or metastatic breast cancer (MBC) with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting

Important Safety Information

Diarrhea occurred in 86% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 90% of patients receiving Verzenio alone in MONARCH 1. Grade 3 diarrhea occurred in 13% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 20% of patients receiving Verzenio alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

In MONARCH 2, diarrhea incidence was greatest during the first month of Verzenio dosing. The median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. Twenty-two percent of patients with diarrhea required a dose omission and 22% required a dose reduction. In the MONARCH 1 study, the time to onset and resolution for diarrhea were similar to those in MONARCH 2.

Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow-up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue Verzenio until toxicity resolves to ≤Grade 1, and then resume Verzenio at the next lower dose.

Neutropenia occurred in 46% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 37% of patients receiving Verzenio alone in MONARCH 1. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 32% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 27% of patients receiving Verzenio in MONARCH 1. In MONARCH 2 and MONARCH 1, the median time to first episode of Grade >3 neutropenia was 29 days, and the median duration of Grade ≥3 neutropenia was 15 days.

Monitor complete blood counts prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Febrile neutropenia has been reported in 1% of patients exposed to Verzenio in MONARCH 2 and MONARCH 1. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

Grade ≥3 **increases in alanine aminotransferase (ALT)** (4% versus 2%) and **aspartate aminotransferase (AST)** (2% versus 3%) were reported in the Verzenio and placebo arms respectively, in MONARCH 2.

In MONARCH 2, for patients receiving Verzenio plus fulvestrant with Grade ≥3 ALT increased, median time to onset was 57 days, and median time to resolution to Grade <3 was 14 days. For patients with Grade ≥3 AST increased, median time to onset was 185 days, and median time to resolution was 13 days.

Please see additional Important Safety Information on adjacent page.

Important Safety Information (cont'd)

For assessment of potential **hepatotoxicity**, monitor liver function tests (LFTs) prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation.

Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus fulvestrant in MONARCH 2 as compared to 0.9% of patients treated with fulvestrant plus placebo. Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Verzenio can cause **fetal harm** when administered to a pregnant woman based on findings from animal studies and the mechanism of action. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Verzenio and for at least 3 weeks after the last dose. There are no data on the presence of Verzenio in human milk or its effects on the breastfed child or on milk production. Advise lactating women not to breastfeed during Verzenio treatment and for at least 3 weeks after the last dose because of the potential for serious adverse reactions in breastfed infants. Based on findings in animals, Verzenio may impair fertility in males of reproductive potential.

The **most common adverse reactions (all grades, ≥10%)** observed in **MONARCH 2 for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant** were diarrhea (86% vs 25%), neutropenia (46% vs 4%), fatigue (46% vs 32%), nausea (45% vs 23%), infections (43% vs 25%), abdominal pain (35% vs 16%), anemia (29% vs 4%), leukopenia (28% vs 2%), decreased appetite (27% vs 12%), vomiting (26% vs 10%), headache (20% vs 15%), dysgeusia (18% vs 3%), thrombocytopenia (16% vs 3%), alopecia (16% vs 2%), stomatitis (15% vs 10%), ALT increased (13% vs 5%), pruritus (13% vs 6%), cough (13% vs 11%), dizziness (12% vs 6%), AST increased (12% vs 7%), peripheral edema (12% vs 7%), creatinine increased (12% vs <1%), rash (11% vs 4%), pyrexia (11% vs 6%), and weight decreased (10% vs 2%).

The **most common adverse reactions (all grades, ≥10%)** observed in **MONARCH 1** with Verzenio were diarrhea (90%), fatigue (65%), nausea (64%), decreased appetite (45%), abdominal pain (39%), neutropenia (37%), vomiting (35%), infections (31%), anemia (25%), thrombocytopenia (20%), headache (20%), cough (19%), leukopenia (17%), constipation (17%), arthralgia (15%), dry mouth (14%), weight decreased (14%), stomatitis (14%), creatinine increased (13%), alopecia (12%), dysgeusia (12%), pyrexia (11%), dizziness (11%), and dehydration (10%).

The **most frequently reported ≥5% Grade 3 or 4 adverse reactions** that occurred in the Verzenio arm of **MONARCH 2** were neutropenia (27% vs 2%), diarrhea (13% vs <1%), leukopenia (9% vs 0%), anemia (7% vs 1%), and infections (6% vs 3%).

The **most frequently reported ≥5% Grade 3 or 4 adverse reactions** from **MONARCH 1** with Verzenio were neutropenia (24%), diarrhea (20%), fatigue (13%), infections (7%), leukopenia (6%), anemia (5%), and nausea (5%).

Lab abnormalities (all grades; Grade 3 or 4) for **MONARCH 2 in ≥10% for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant** were increased serum creatinine (98% vs 74%; 1% vs 0%), decreased white blood cells (90% vs 33%; 23% vs 1%), decreased neutrophil count (87% vs 30%; 33% vs 4%), anemia (84% vs 33%; 3% vs <1%), decreased lymphocyte count (63% vs 32%; 12% vs 2%), decreased platelet count (53% vs 15%; 2% vs 0%), increased ALT (41% vs 32%; 5% vs 1%), increased AST (37% vs 25%; 4% vs 4%).

Lab abnormalities (all grades; Grade 3 or 4) for MONARCH 1 with Verzenio were increased serum creatinine (98%; <1%), decreased white blood cells (91%; 28%), decreased neutrophil count (88%; 27%), anemia (68%; 0%), decreased lymphocyte count (42%; 14%), decreased platelet count (41%; 2%), increased ALT (31%; 3%), and increased AST (30%; 4%).

Strong CYP3A inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity. Avoid concomitant use of ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold. In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the Verzenio dose to 100 mg twice daily with concomitant use of other strong CYP3A inhibitors. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the Verzenio dose to 50 mg twice daily with concomitant use of other strong CYP3A inhibitors. If a patient taking Verzenio discontinues a strong CYP3A inhibitor, increase the Verzenio dose (after 3 to 5 half-lives of the inhibitor) to the dose that was used before starting the strong inhibitor. Patients should avoid grapefruit products.

Avoid concomitant use of strong CYP3A inducers and consider alternative agents. Coadministration of Verzenio with rifampin, a strong CYP3A inducer, decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity.

With severe hepatic impairment (Child-Pugh Class C), reduce the Verzenio dosing frequency to once daily. The pharmacokinetics of Verzenio in patients with **severe renal impairment** (CLcr <30 mL/min), end stage renal disease, or in patients on dialysis **is unknown.** No dosage adjustments are necessary in patients with mild or moderate hepatic (Child-Pugh A or B) and/or renal impairment (CLcr ≥30-89 mL/min).

Please see Brief Summary of full Prescribing Information for Verzenio on next pages.

AL HCP ISI 02OCT2017

Reference: 1. Verzenio [package insert]. Indianapolis, IN: Eli Lilly and Company; 2017.

VERZENIO™ (abemaciclib) tablets, for oral use
Initial U.S. Approval: 2017

BRIEF SUMMARY: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE

VERZENIO™ (abemaciclib) is indicated:

- in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.
- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Diarrhea

Diarrhea occurred in 86% of patients receiving VERZENIO plus fulvestrant in MONARCH 2 and 90% of patients receiving VERZENIO alone in MONARCH 1. Grade 3 diarrhea occurred in 13% of patients receiving VERZENIO plus fulvestrant in MONARCH 2 and in 20% of patients receiving VERZENIO alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

In MONARCH 2, diarrhea incidence was greatest during the first month of VERZENIO dosing. The median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. Twenty-two percent of patients with diarrhea required a dose omission and 22% required a dose reduction. In the MONARCH 1 study, the time to onset and resolution for diarrhea were similar to those in MONARCH 2.

Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue VERZENIO until toxicity resolves to ≤Grade 1, and then resume VERZENIO at the next lower dose.

Neutropenia

Neutropenia occurred in 46% of patients receiving VERZENIO plus fulvestrant in MONARCH 2 and 37% of patients receiving VERZENIO alone in MONARCH 1. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 32% of patients receiving VERZENIO plus fulvestrant in MONARCH 2 and in 27% of patients receiving VERZENIO in MONARCH 1. In MONARCH 2 and MONARCH 1, the median time to first episode of Grade >3 neutropenia was 29 days, and the median duration of Grade ≥3 neutropenia was 15 days.

Monitor complete blood counts prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Febrile neutropenia has been reported in 1% of patients exposed to VERZENIO in MONARCH 2 and MONARCH 1. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

Hepatotoxicity

In MONARCH 2, Grade ≥3 increases in ALT (4% versus 2%) and AST (2% versus 3%) were reported in the VERZENIO and placebo arms, respectively.

In MONARCH 2, for patients receiving VERZENIO plus fulvestrant with Grade ≥3 ALT increased, median time to onset was 57 days, and median time to resolution to Grade <3 was 14 days. For patients with Grade ≥3 AST increased, median time to onset was 185 days, and median time to resolution was 13 days.

Monitor liver function tests (LFTs) prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation.

Venous Thromboembolism

In MONARCH 2, venous thromboembolic events were reported in 5% of patients treated with VERZENIO plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo. Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with VERZENIO and for at least 3 weeks after the last dose.

ADVERSE REACTIONS

Clinical Studies 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.

MONARCH 2: VERZENIO in Combination with Fulvestrant

Women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy

The safety of VERZENIO (150 mg twice daily) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in MONARCH 2. The data described below reflect exposure to VERZENIO in 441 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of VERZENIO plus fulvestrant in MONARCH 2.

Median duration of treatment was 12 months for patients receiving VERZENIO plus fulvestrant and 8 months for patients receiving placebo plus fulvestrant.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving VERZENIO plus fulvestrant. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. VERZENIO dose reductions due to diarrhea of any grade occurred in 19% of patients receiving VERZENIO plus fulvestrant compared to 0.4% of patients receiving placebo and fulvestrant. VERZENIO dose reductions due to neutropenia of any grade occurred in 10% of patients receiving VERZENIO plus fulvestrant compared to no patients receiving placebo plus fulvestrant.

Permanent study treatment discontinuation due to an adverse event was reported in 9% of patients receiving VERZENIO plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Adverse reactions leading to permanent discontinuation for patients receiving VERZENIO plus fulvestrant were infection (2%), diarrhea (1%), hepatotoxicity (1%), fatigue (0.7%), nausea (0.2%), abdominal pain (0.2%), acute kidney injury (0.2%), and cerebral infarction (0.2%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 18 cases (4%) of VERZENIO plus fulvestrant treated patients versus 10 cases (5%) of placebo plus fulvestrant treated patients. Causes of death for patients receiving VERZENIO plus fulvestrant included: 7 (2%) patient deaths due to underlying disease, 4 (0.9%) due to sepsis, 2 (0.5%) due to pneumonitis, 2 (0.5%) due to hepatotoxicity, and one (0.2%) due to cerebral infarction.

The most common adverse reactions reported (≥20%) in the VERZENIO arm were diarrhea, fatigue, neutropenia, nausea, infections, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache (Table 1). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, anemia, and infections.

Table 1: Adverse Reactions ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

	VERZENIO plus Fulvestrant N=441			Placebo plus Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Diarrhea	86	13	0	25	<1	0
Nausea	45	3	0	23	1	0
Abdominal Pain[a]	35	2	0	16	1	0
Vomiting	26	<1	0	10	2	0
Stomatitis	15	<1	0	10	0	0
Infections and Infestations						
Infections[b]	43	5	<1	25	3	<1
Blood and Lymphatic System Disorders						
Neutropenia[c]	46	24	3	4	1	<1
Anemia[d]	29	7	<1	4	1	0
Leukopenia[e]	28	9	<1	2	0	0
Thrombocytopenia[f]	16	2	1	3	0	<1
General Disorders and Administration Site Conditions						
Fatigue[g]	46	3	0	32	<1	0
Edema peripheral	12	0	0	7	0	0
Pyrexia	11	<1	<1	6	<1	0
Metabolism and Nutrition Disorders						
Decreased appetite	27	1	0	12	<1	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	13	0	0	11	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	16	0	0	2	0	0
Pruritus	13	0	0	6	0	0
Rash	11	1	0	4	0	0
Nervous System Disorders						
Headache	20	1	0	15	<1	0
Dysgeusia	18	0	0	3	0	0
Dizziness	12	1	0	6	0	0
Investigations						
Alanine aminotransferase increased	13	4	<1	5	2	0
Aspartate aminotransferase increased	12	2	0	7	3	0
Creatinine increased	12	<1	0	<1	0	0
Weight decreased	10	<1	0	2	<1	0

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness.
[b] Includes upper respiratory tract infection, urinary tract infection, lung infection, pharyngitis, conjunctivitis, sinusitis, vaginal infection, sepsis.
[c] Includes neutropenia, neutrophil count decreased.
[d] Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.
[e] Includes leukopenia, white blood cell count decreased.
[f] Includes platelet count decreased, thrombocytopenia.
[g] Includes asthenia, fatigue.

Additional adverse reactions in MONARCH 2 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, subclavian vein thrombosis, axillary vein thrombosis, and DVT inferior vena cava), which were reported in 5% of patients treated with VERZENIO plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo.

Table 2: Laboratory Abnormalities ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

	VERZENIO plus Fulvestrant N=441			Placebo plus Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Creatinine increased	98	1	0	74	0	0
White blood cell decreased	90	23	<1	33	<1	0
Neutrophil count decreased	87	29	4	30	4	<1
Anemia	84	3	0	33	<1	0
Lymphocyte count decreased	63	12	<1	32	2	0
Platelet count decreased	53	<1	1	15	0	0
Alanine aminotransferase increased	41	4	<1	32	1	0
Aspartate aminotransferase increased	37	4	0	25	4	<1

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. In clinical studies, increases in serum creatinine (mean increase, 0.2 mg/dL) occurred within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated glomerular filtration rate (GFR), which are not based on creatinine, may be considered to determine whether renal function is impaired.

VERZENIO™ (abemaciclib) tablets, for oral use AL HCP BS 28SEP2017

VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)

Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting

Safety data below are based on MONARCH 1, a single-arm, open-label, multicenter study in 132 women with measurable HR+, HER2- metastatic breast cancer. Patients received 200 mg VERZENIO orally twice daily until development of progressive disease or unmanageable toxicity. Median duration of treatment was 4.5 months.

Ten patients (8%) discontinued study treatment from adverse reactions due to (1 patient each) abdominal pain, arterial thrombosis, aspartate aminotransferase (AST) increased, blood creatinine increased, chronic kidney disease, diarrhea, ECG QT prolonged, fatigue, hip fracture, and lymphopenia. Forty-nine percent of patients had dose reductions due to an adverse reaction. The most frequent adverse reactions that led to dose reductions were diarrhea (20%), neutropenia (11%), and fatigue (9%).

Deaths during treatment or during the 30-day follow up were reported in 2% of patients. Cause of death in these patients was due to infection.

The most common reported adverse reactions (≥20%) were diarrhea, fatigue, nausea, decreased appetite, abdominal pain, neutropenia, vomiting, infections, anemia, headache, and thrombocytopenia (Table 3). Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib.

Table 3: Adverse Reactions (≥10% of Patients) in MONARCH 1

	VERZENIO N=132		
	All Grades %	**Grade 3 %**	**Grade 4 %**
Gastrointestinal Disorders			
Diarrhea	90	20	0
Nausea	64	5	0
Abdominal pain	39	2	0
Vomiting	35	2	0
Constipation	17	<1	0
Dry mouth	14	0	0
Stomatitis	14	0	0
Infections and Infestations			
Infections	31	5	2
General Disorders and Administration Site Conditions			
Fatigue[a]	65	13	0
Pyrexia	11	0	0
Blood and Lymphatic System Disorders			
Neutropenia[b]	37	19	5
Anemia[c]	25	5	0
Thrombocytopenia[d]	20	4	0
Leukopenia[e]	17	5	<1
Metabolism and Nutrition Disorders			
Decreased appetite	45	3	0
Dehydration	10	2	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	19	0	0
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	15	0	0
Nervous System Disorders			
Headache	20	0	0
Dysgeusia	12	0	0
Dizziness	11	0	0
Skin and Subcutaneous Tissue Disorders			
Alopecia	12	0	0
Investigations			
Creatinine increased	13	<1	0
Weight decreased	14	0	0

[a] Includes asthenia, fatigue.
[b] Includes neutropenia, neutrophil count decreased.
[c] Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.
[d] Includes platelet count decreased, thrombocytopenia.
[e] Includes leukopenia, white blood cell count decreased.

Table 4: Laboratory Abnormalities for Patients Receiving VERZENIO in MONARCH 1

	VERZENIO N=132		
	All Grades %	**Grade 3 %**	**Grade 4 %**
Creatinine increased	98	<1	0
White blood cell decreased	91	28	0
Neutrophil count decreased	88	22	5
Anemia	68	0	0
Lymphocyte count decreased	42	13	<1
Platelet count decreased	41	2	0
ALT increased	31	3	0
AST increased	30	4	0

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. In clinical studies, increases in serum creatinine (mean increase, 0.3 mg/dL) occurred within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated GFR, which are not based on creatinine, may be considered to determine whether renal function is impaired.

DRUG INTERACTIONS

Effect of Other Drugs on VERZENIO

Strong CYP3A Inhibitors

Strong CYP3A inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity.

Ketoconazole

Avoid concomitant use of ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold.

Other Strong CYP3A Inhibitors

In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the VERZENIO dose to 100 mg twice daily with concomitant use of other strong CYP3A inhibitors. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the VERZENIO dose to 50 mg twice daily with concomitant use of other strong CYP3A inhibitors. If a patient taking VERZENIO discontinues a strong CYP3A inhibitor, increase the VERZENIO dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the strong inhibitor. Patients should avoid grapefruit products.

Strong CYP3A Inducers

Coadministration of VERZENIO with rifampin, a strong CYP3A inducer, decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity. Avoid concomitant use of strong CYP3A inducers and consider alternative agents.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. In animal reproduction studies, administration of abemaciclib during organogenesis was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on AUC at the maximum recommended human dose (*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 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.

Data

Animal Data

In an embryo-fetal development study, pregnant rats received oral doses of abemaciclib up to 15 mg/kg/day during the period of organogenesis. Doses ≥4 mg/kg/day caused decreased fetal body weights and increased incidence of cardiovascular and skeletal malformations and variations. These findings included absent innominate artery and aortic arch, malpositioned subclavian artery, unossified sternebra, bipartite ossification of thoracic centrum, and rudimentary or nodulated ribs. At 4 mg/kg/day in rats, the maternal systemic exposures were approximately equal to the human exposure (AUC) at the recommended dose.

Lactation

Risk Summary

There are no data on the presence of abemaciclib in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed infants from VERZENIO, advise lactating women not to breastfeed during VERZENIO treatment and for at least 3 weeks after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal studies, VERZENIO can cause fetal harm when administered to a pregnant woman. Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with VERZENIO.

Contraception

Females

VERZENIO can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during VERZENIO treatment and for at least 3 weeks after the last dose.

Infertility

Males

Based on findings in animals, VERZENIO may impair fertility in males of reproductive potential.

Pediatric Use

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

Geriatric Use

Of the 441 patients who received VERZENIO in MONARCH 2, 35% were 65 years of age or older and 9% were 75 years of age or older. Of the 132 patients who received VERZENIO in MONARCH 1, 32% were 65 years of age or older and 8% were 75 years of age or older. No overall differences in safety or effectiveness of VERZENIO were observed between these patients and younger patients.

Renal Impairment

No dosage adjustment is required for patients with mild or moderate renal impairment (CLcr ≥30-89 mL/min, estimated by Cockcroft-Gault [C-G]). The pharmacokinetics of abemaciclib in patients with severe renal impairment (CLcr <30 mL/min, C-G), end stage renal disease, or in patients on dialysis is unknown.

Hepatic Impairment

No dosage adjustments are necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B). Reduce the dosing frequency when administering VERZENIO to patients with severe hepatic impairment.

OVERDOSAGE

There is no known antidote for VERZENIO. The treatment of overdose of VERZENIO should consist of general supportive measures.

Rx only.

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

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SPECIAL ISSUE / Technology in Cancer Care
DECEMBER 2017
VOLUME 23, ISSUE 13

PROVIDER PERSPECTIVE

SP511

Can the Digital Revolution Empower the Move Toward Value-Based Cancer Care?

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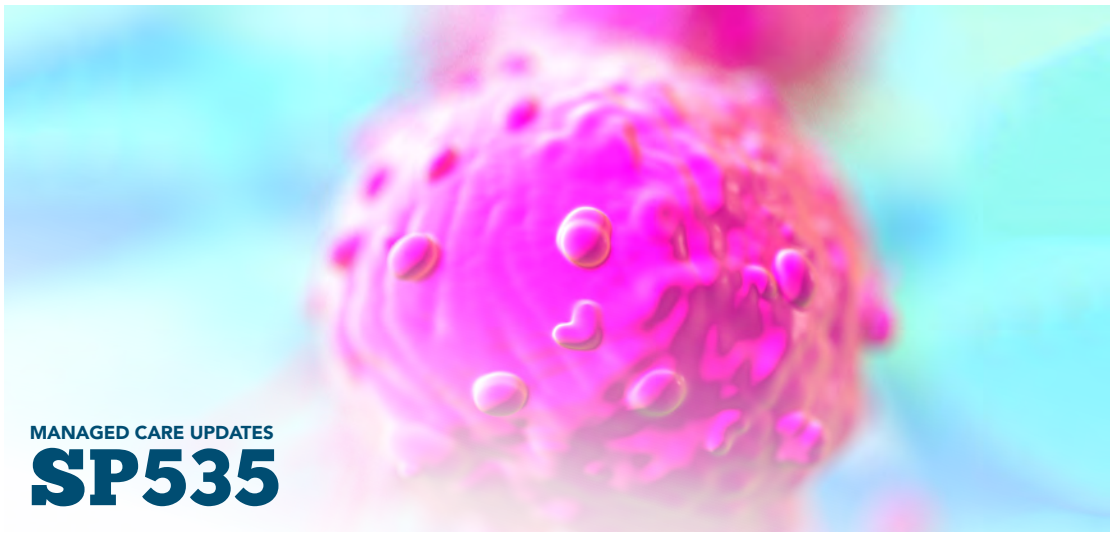

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FROM THE CHAIRMAN

Technology in Healthcare: You Win Some You Lose Some


HENNESSY

TECHNOLOGY UPGRADES ARE a plus in any field—they can quicken processes, aid documentation, and give users the ability to gain feedback. In the healthcare world, too, the current push to implement value-based care has required practices and healthcare systems to ensure workflows are faster and interactive, with feedback that can be used for quality reporting and benchmarking.

Several technology companies offer capabilities that can improve existing electronic health records (EHRs) and help practices improve care delivery, analysis, and reporting; some of these platforms can also be individualized to serve specific clinic needs.

Flatiron Health, for example, has developed workflow systems that can streamline EHRs, help analyze quality measurement and claims data, and also provide clinicians the ability to screen patients for clinical trials. The company has developed a technology suite specifically for community practices that can help them adopt capabilities to succeed with new payment models such as CMS' Oncology Care Model (OCM) pilot.

Another firm promoting technology adoption is Integra Connect. As practices are forced to take on responsibility for their patients' overall health, technologies and capabilities at the point of care are the primary means of ensuring their success. In this issue, authors from Integra point out that OCM participants have identified 3 primary drivers of cost and quality that affect patients: emergency department visits, unnecessary inpatient admissions, and end-of-life care. They indicate that changes to the core workflow can help improve efficiency and lower cost, and care coordination can be a very important tool in this process, as indicated by a case study that the authors share.

Technology, in the form of social media, has had another interesting influence on improving access to care—in the form of clinical trial recruitment. As Mary Caffrey notes in her article, companies, such as Clara Health and Seeker Health, are using social media and other tools to connect researchers with eligible patients. The success of these tools is evident from the fact that researchers are able to reach patients from geographical rural locations as well as more individuals that belong to minority populations.

However, the transition from paper-based to electronic-based office records has its drawbacks, as former medical director with Aetna, Sheree Starrett, MD, MS, points out. Physicians, according to Starrett, are spending more time doing data entry in the exam room, which has changed their relationship with the patient. In her article, she recommends ways in which physicians can avoid the screen from being a hindrance in their connection with the patient.

We hope this last issue of 2017 continues the patient-centered conversations that we held throughout the year. Please be on the lookout for a recap issue of our Patient-Centered Oncology Care® meeting, which we will publish in February 2018.

As always, thank you to our readers for their continued support and we at *The American Journal of Managed Care®* would like to wish everyone a wonderful New Year! ◆

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

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FROM THE EDITOR-IN-CHIEF

Back to the Future

OVER THE PAST SEVERAL YEARS the nature of cancer care has evolved in dramatic, sometimes breathtaking, ways. Since I began caring for patients with cancer, more than 2 decades ago, our paradigm for delivering care has evolved dramatically from the mind-set of boldly pushing the limits of dose/therapeutic intensity (more intensive chemotherapy, more radical surgery, and more intensive radiotherapeutic dosing schemes) toward an era of targeted therapeutics where genomic information and precision medicine–based treatment paradigms provide clinicians and patients with heretofore unimaginable, increasingly effective treatment options.


ALVARNAS

As we circle back to look at cancer care from this exciting, innovation-based perspective, the wealth of meaningful emerging therapeutic technologies (immunotherapeutic agents and chimeric antigen receptor T cells) and the growing role of nonphysician care providers and resources (pharmacists, pharmacy benefits managers, care coordinators, and navigators) have opened the door to more patient-centered care; however, these advances have also provoked concerns about how this breadth of services can be sustainably delivered. As annual American healthcare expenditures repeatedly break the previous year's record and the inflation rate for cancer care outpaces the rate for the overall economic by nearly 10-fold, the challenge of ensuring that cancer care innovations can be delivered equitably, at scale, and with high quality and consistency becomes an increasingly daunting, seemingly impossible, challenge.

> *"We shall not cease from exploration*
> *And the end of all our exploring*
> *Will be to arrive where we started*
> *And know the place for the first time."*
>
> — Little Gidding
> T.S. Eliot

While I am far too skeptical to believe that technology can save us from this conundrum, I do believe wholeheartedly that the key to understanding value delivery in cancer care will require data inputs from a transformational set of technology-based tools that will help bring greater clarity to how we understand, and empower, opportunities for ensuring more effective, value-based cancer care. There is a wealth of data, far beyond what exists in our paper charts or electronic health records that could help us better understand how best to apply genomic diagnostic technologies, sequence therapeutic options (including targeted therapeutic agents), and deliver this type of care at scale. The big data model of healthcare analytics could, if applied correctly, help us evolve our cancer care delivery system in ways that are both fiscally responsible and clinically effective. This issue of *Evidence-Based Oncology*™ (*EBO*™) reviews the role of technology in the cancer care domain.

As patients and their families face their cancer journeys, the extraordinary changes in cancer care delivery—through therapeutic innovation and better risk assessment—promise greater opportunities for cures, more effective symptom management, and a better quality of life as cancer survivors. Over the past year, *EBO*™ has tried to show how the cancer care landscape is challenging. We do so in the optimistic belief that by engaging the breadth of cancer care stakeholders, the challenge of delivering equitable, safe, timely, effective, cost-efficient, increasingly patient-centered cancer care, can become an enduring reality.

On behalf of myself and the editorial staff, I wish you and your families a wonderful holiday season and a happy New Year. ◆

Joseph Alvarnas, MD
Editor-in-Chief

EDITORIAL MISSION

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

Halt and Catch Fire: Can the Digital Revolution Empower the Move Toward Value-Based Cancer Care?

Joseph Alvarnas, MD

FROM THE AFFORDABLE CARE ACT[1] to countless pieces in the *New England Journal of Medicine*,[2,3] the consensus of thought leaders from academia, government, and industry recognizes the need to shift from a fee-for-service model toward a more coherent system of predicating payment on value delivery. In 2015, the national healthcare expenditures in the United States rose to $3.2 trillion, which accounted for 17.8% of the American gross domestic product.[4] The push toward value-based care delivery is largely driven by the unsustainable growth rate of healthcare expenditures and the underwhelming American healthcare outcomes that result despite this extraordinary expenditure rate.[5]

There is no shortage of academic, industry, and government sources that identify value as equaling cost/outcomes; there is far less uniformity of opinion when it comes to defining what that means for a particular patient affected by cancer.

The value conundrum is particularly challenging within the domain of cancer care, in which treatment-related costs dwarf overall healthcare spending: According to estimates from the National Cancer Institute, cancer care-related costs are projected to grow by 39% ($172.8 billion) by 2020.[6] Pharmaceuticals and therapeutic innovation wield an extraordinary impact on these costs—cancer drug spending was estimated at $37.8 billion in 2016, which represents a 33% increase ($9.4 billion) for new drugs alone since 2010.[7] The growth of genomic technologies (including somatic and germ line testing) will further inflate cancer care costs; the current world market for genomic testing is $9.2 billion and is expected to grow to more than $20 billion by 2022.[8]

The move toward developing transparency around value delivery in cancer care is undermined by 3 key factors:

1. The lack of a national data set for assessing cancer outcomes data, on either a provider or institutional basis, that is available for performance comparison purposes. While the Center for International Bone Marrow Transplant Research routinely provides risk-adjusted survival outcomes data to consumers, these data are limited to only those patients who undergo allogeneic transplantation.[9]
2. Coding and billing data lack sufficient data richness to adequately risk-stratify cancer patients in a manner that allows for a transparent assessment of cancer outcomes and costs as related to clinical risk.[10]
3. As our healthcare system increasingly works to reduce costs by commoditizing services such as laboratory testing (including genomic testing), imaging studies, and therapeutic delivery (through an increased reliance upon specialty pharmacy services and third-party pharmacy benefit managers), it becomes increasingly difficult for cancer care providers to understand their own care delivery costs because of the balkanization of health records and the proprietary nature of many data sources.

There is no shortage of academic, industry, and government sources that identify value as equaling cost/outcomes; there is far less uniformity of opinion when it comes to defining what that means for a particular patient affected by cancer. Many of the current "value" models for cancer care delivery look for the value of isolated »

healthcare decisions/transactions rather than the aggregate costs/outcomes of the delivery model.[11,12]

It is no longer adequate to simply aggregate data by histological diagnoses. In this modern era, patients are defined with increasing precision (hence the *EGFR*-negative, *ALK*-negative patient who expresses PD-L1 for whom the predicted cost of care is far more predicable); the goal then becomes one of defining the risk-banded costs of care based on a level of data richness and analytics that defies the capacities of most electronic health records (EHRs) or the analytical capacities of most healthcare providers and cancer care delivery networks. This level of iterative risk/cost model evolution needs a depth of data that is largely unprecedented in healthcare today. These analytics must have the ability to incorporate a multiplicity of data sources, reconcile multiple identifiers for a single patient, and simultaneously leverage an evolving data set of genomic risk factors.

This seemingly impossible task now represents a key focus of several efforts that attempt to master/reconcile the breadth of relevant care delivery data in the pursuit of increasing transparent, data-rich models for assessing care. The American Society of Clinical Oncology (ASCO) has published an updated version of its value framework that has evolved to include more data sources and better integration into decision support tools to ensure that this construct can be employed more consistently in care delivery.[13] The meaningfulness of decision support tools and outcomes analytics will, however, require a profoundly different information architecture to ensure that such systems are based on sufficiently rich data resources, are meaningful, and can base data assessments on an accurate risk segmentation of the population in question.

This level of analytic capacity must be based on the big data model of information technology. In their recently published book chapter, "Big Data Analytics in Healthcare: A Cloud-Based Framework for Generating Insights," Anjum et al, envision a move toward systems that utilize scalable cloud-based data analytics architecture. They argue that to be effective, these cloud-based systems will need to ensure that genomic and clinical data are correctly identified and linked while ensuring that data from a diverse array of sources, systems, and "disparate locations" are aggregated in a robust, quality-controlled manner.[14]

A robust big data analytics model in the cancer care domain can yield the following potential benefits:

- Clinical trials matching
- Increasingly precise patient risk segmentation
- More robust cost/risk assessments
- A tool for more transparent value mapping of genomic/precision medicine care delivery

Toward that end, several vendors have entered the marketplace with models and tools directed at making this quantum leap toward more meaningful value-based analytics. ASCO's big data informatics model, CancerLinQ, intends to provide both practice and research planning tools that leverage data in an innovative way that far exceeds the analytical capacities of the typical EHR system.[15] Other vendors have entered the market space with propriety big data–based analytical systems, which include products and services from Flatiron Health[16] and Cota Healthcare.[17] These products are marketed as tools for value-based data analytics for clinical practice, research planning, and revenue cycle management.

The meaningfulness of decision support tools and outcomes analytics will require a profoundly different information architecture to ensure that such systems are based on sufficiently rich data resources, are meaningful, and can base data assessments on an accurate risk segmentation of the population in question.

Recently, the importance of these new analytical service tools platforms has been highlighted by the inclusion of the Cota Healthcare system as a key part of the Oncology Physician-Focused Payment Model (PFPM) submitted by Hackensack Meridian Health. The PFPM Technical Advisory Committee did ultimately recommend to the HHS secretary that the proposed oncology bundled payment model (which uses Cota's CNA-Guided [Cota Nodal Address] Care to establish risk-cost bands within the bundles) should be accepted for testing as a pilot advanced alternative payment model (AAPM).[18] This AAPM approval was followed shortly thereafter by an announcement from Memorial Sloan Kettering Cancer Center and Cota Healthcare regarding a 5-year exclusive deal in which these 2 entities would collaborate on projects focused on leveraging this suite of big data analytics to bring more effective precision medicine solutions to patients with cancer.[19]

The growing intensive information demands of the new precision medicine paradigm of cancer care, coupled with the drive to achieve a more meaningful alignment between cancer risk and the cost of care, is likely to increasingly push big data technologies to the forefront of cancer care. As the "black box" paradigm of per-capita reductions in the cost of care articulated in the "Triple Aim of Care"[20] is challenged by new cancer care diagnostic and therapeutic technologies, big data analytic solutions can help to create a far more transparent and meaningful paradigm for how we can more intelligently move toward more value-based care for cancer patients. ◆

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TECHNOLOGY PLATFORM

High-Impact Workflow Changes for Value-Based Care Success

Charles Saunders, MD; Charles Alcorn, MS; Catherine Cowan, MSN, RN; and Maria Fabbiano, RN

SAUNDERS

ALCORN

Charles Saunders, MD, is CEO at Integra Connect.

Charles Alcorn, MS, is senior director of medical economics, Integra Connect.

Value-Based Care Drives Practice Transformation

In this era of value-based care, oncologists are becoming increasingly accountable for achieving improvements in cost, quality, and experience across their patient populations. This expectation is at the foundation of measures introduced by CMS through both the Merit-based Incentive Payment System (MIPS) and the Oncology Care Model (OCM) alternative payment model programs—with commercial payers following suit. It is essential to the financial viability of oncology practices that they perform well against these evolving rules. At stake is a swing in reimbursement of 28% or more.[1] The precise rate depends on the value-based care programs that practices choose and their performance, relative to peers, on the required measures.

These new innovative payment models challenge oncologists to assume an unprecedented degree of responsibility for their patients' entire episodes of care. However, this is a departure from the way most practices have traditionally operated, and nothing short of clinical, financial, and operational transformation will be needed to succeed. The OCM anticipated this and provided its road map in the form of 7 mandatory pillars of practice transformation, from enhanced patient access and evidence-based treatment guidelines to the introduction of care management.[2] It then attempted to mitigate the infrastructure and investment requirements through Monthly Enhanced Oncology Services payments aligned with episodes of care on a per member per month basis.

A North Star for Success

Despite these guide posts, many practices have struggled with where to start and how to prioritize the highest-impact interventions, understandably so, given the number of potential focus areas and the uncharted territory in front of them. An emerging group of OCM participants has coalesced around a common vision to guide their transition to value-based care—increasing direct control over the 3 primary drivers of cost and quality that impact patients:

- **Avoidable emergency department (ED) visits**. These are often triggered when a patient with an acute complaint cannot access their oncologist and goes (or is directed) to the hospital instead. Our review of CMS data spanning a wide range of OCM practices during a period of 3.5 years found that a single ED visit ($729.67) costs nearly 6 times more than an average office visit ($124.67) and often results in an admission.
- **Unnecessary inpatient admissions**. Usually these result from patients presenting at the ED and clinicians admitting them based on an incomplete picture of their conditions and treatment. Our data show that nearly half of ED visits resulted in an admission that cost an average of $9797.
- **End-of-life care**. This becomes important when a patient in an irrevocably advanced disease state continues to receive treatment without an awareness of other options for care. Multi-pronged programs to support seriously ill patients with case management, advanced care planning information, and tools—in the form of government and community resources—have resulted in substantial improvements in patient experience and cost. For example, Aetna's Compassionate Care Program[3] yielded a 3-fold increase in the hospice election rate, which not only fueled higher patient satisfaction, but reduced acute days by 82%, ED visits by 75%, and intensive care unit stays by 86%.

How can practices most effectively move the needle against these pitfalls of cost and quality? While there are many options for interventions and supporting decisions to be made along the way—staffing models, clinical protocols, and resources—the connective tissue is workflow. Specifically, 4 core workflow changes are being pursued by early leaders in the OCM program, enabled by new technologies:

1. Identifying and stratifying patient populations on an ongoing basis
2. Employing targeted care coordination and management
3. Improving patient access to appropriate levels of care
4. Deploying end-of-life and supportive care programs

Identify and Stratify Patient Populations on an Ongoing Basis

To reduce costs and improve outcomes, oncologists must begin by identifying and targeting their highest-risk patients and practices must simultaneously deliver programs that prevent low- or moderate-risk patients from becoming high risk. Therefore, practices must have the capability to risk stratify all patients in their panel on a timely and regular basis, not only at the outset of OCM or MIPS participation.

For the typical oncology practice panel, there is a powerful correlation between risk and cost. Analysis of our data acquired from a wide range of OCM practices nationwide demonstrates that 20% of patients account for as much as 50% of total healthcare costs. Many of the costs for the highest-risk group of oncology patients result from emergency medical admissions, 30-day readmissions, and skilled nursing facility stays following hospitalization—a large percentage of which are potentially avoidable.

Few oncology practices have the technologies, skills, and capabilities to undertake this effort on their own. Several leading OCM practices are tackling this challenge by employing sophisticated algorithms and multi-variable statistical models from Integra Connect.

Developed using regression or machine learning techniques, or both, these models account for patient-specific factors, such as:

- Cancer type
- Comorbidities
- Use of chemotherapy agents with serious adverse effects
- Number of chemotherapy agents
- Functional status

The result has been grouping patients into risk cohorts based on their likelihood of having 1 or more potentially avoidable high-cost events. Only then can practices predict the likelihood of adverse events and design effective interventions in a less-costly, lower-acuity setting such as the office itself.

However, these leaders are converting measurement and management into an ongoing workflow tied to the core operations of their practices. Why? A patient's risk profile may change very quickly with the advancement of their cancer or the addition or change of a chemotherapeutic agent, with serious side effects. Therefore, patients must be risk stratified as early as possible at the start of an episode of care or when their cancer is first diagnosed and treated with one or more chemotherapeutic agents. The stratification must then be updated on a regular basis to ensure it accurately reflects the most current status of the patient's health. then updated frequently.

Establishing this workflow relies on consistent access to a wide variety of data—clinical, financial, and social—that must be scrubbed, identity-matched, and semantically normalized to enable "whole" patient views that support subsequent analysis for predictive risk.

Employ Targeted Care Coordination and Management

With their highest-risk patients identified, practices can effectively target them with proven interventions. Care management is a long-standing concept that, until the advent of value-based care among practices, was associated with health insurers in the managed care industry. Its premise was that care activities that occurred in between office visits, such as telephonic outreach for a follow-up or a status check with patients and/or their caregivers, would proactively allow for early identification and resolution of health and socioeconomic issues that could result in unnecessary utilization of costly services, such as the ED or hospital, if left untreated.

Now, with value-based models requiring a whole patient approach, some OCM practices are rapidly developing effective and efficient care management and navigation capabilities. Although oncologists and their clinical staff may have performed some elements of care management in the past, these actions were secondary to their traditional role, which is managing the patients' specific chief complaint in an office-based setting. The nature of fee-for-service reimbursement encouraged this episodic approach to care and discouraged activities outside of the office encounter. Now, OCM practices are organizing and staffing dedicated care management programs and integrating them into high-risk patient workflow. Their keys to successful transformation have included:

Technology that allows oncologists to stratify patients by level of risk can be used to standardize emergency department (ED) protocols and target patients who visit the ED frequently with acute complaints.

- Recognizing that care management activities are complex and contain new responsibilities that require time and resources to execute well; they cannot simply be added to the workload of a practice's existing staff
- Ensuring sufficient staffing to achieve the desired results, with capacity driven by the number of patients being managed in the context of their clinical risk, behavioral health needs, and socioeconomic factors, which are strong predictors of utilization
- Developing a staff mix of licensure levels (registered nurse, licensed practical nurse, certified management accountant, social worker, etc) to allow staff to operate at the top of their license in a team-based approach to care, which contributes to an efficient and cost-effective care management program
- Utilizing an application/program that provides required tools for assessment, care planning, intuitive patient care management activities, and communication with the patient's interdisciplinary care team.

To understand the positive clinical and financial effects of care management, consider the following example from an OCM practice. A care navigator contacted an 80-year-old man with a diagnosis of prostate cancer for a regularly scheduled follow-up status check. She found that the patient was not planning to fill his prescription because he could not afford it. The care navigator, with the patient, contacted a patient advocate and obtained financial assistance so the patient could pay for his medication and become compliant. Without this intervention, the lack of adherence might not have been identified until symptom progression.

Improve Patient Access to Appropriate Levels of Care

Care management represents a new and proactive workflow for many practices. Care teams must also transform their daily routines to react more efficiently and effectively to unforeseen events.

One critical dimension of these efforts is ensuring patient access to the appropriate level of care at the appropriate time. Previously, provider access was dictated by the standard work week: the open hours of the physical office setting. Yet, patient concerns arise 24 hours a day, 7 days a week.

As a result, a pattern of access behavior was established that shuttled the patient to the acute care environment and resulted in admission regardless of patient needs or acuity. Unfortunately,

What often remains unappreciated is that for oncology patients, every acute complaint is interpreted as an emergency. Thus, practices are undertaking multiple activities to shape acute care utilization for nonemergent care.

although financial incentives further encourage acute care admission in many US markets, practices also bear responsibility by providing contradictory messaging and few options to patients. For example, patient messaging is ubiquitous and includes the instruction "if you have a medical emergency, hang up and call 911." What often remains unappreciated is that for oncology patients, every acute complaint is interpreted as an emergency. Thus, practices are undertaking multiple activities to shape acute care utilization for nonemergent care. These conditions frequently include constipation, urinary tract infection, fatigue, malaise, weakness, anemia, respiratory infections, dehydration, nausea, and vomiting. These conditions are highly amenable to ambulatory care interventions and generally do not require acute care services.

To redirect patients to the correct site of care, one group of OCM practices conducted organized audits of their messaging for clarity and consistency to deduce appropriate next steps for patients with »


COWAN


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acute complaints. This entailed a methodical examination of all patient-facing materials and talk tracks, including brochures, answering service messaging, on-hold messaging, handouts, websites, and any other promotional materials. Post audit, all 911 messaging was revised by:

- Defining "emergency" in all patient materials
- Removing prior 911 messaging and having the patient contact the oncology practice before access to acute care
- Diminishing the placement of the messaging, as appropriate

Other productive interventions included efforts to actively direct the patient to the appropriate level of care. Administrators established practice orientation classes as part of the new patient process, with handouts detailing how to handle emergencies and stressing that patients contact their oncologist before proceeding to acute care, along with outlining the dangers of unnecessary acute care utilization, including ED exposure to pathogens, especially for the neutropenic patient. Many practices have also provided patient wrist bands with the practice phone number to remind patients to call them first. Finally, practices have re-engineered their own patient-facing workflows through the adoption of purpose-built symptom management protocols, such as those developed for the COME HOME program and subsequently expanded by Innovative Oncology Business Solutions—resulting in documented improvements in cost of care.

Other important interventions include:

- Expanding office hours to make it easier for patients to be seen faster and per their convenience
- Establishing relationships with local urgent care facilities to appropriately direct incoming patients
- Standardizing ED protocols with local hospital partners to better recognize and respond to the needs of the practice's patients
- Aiming highly targeted case management at so-called frequent flyers who repeatedly visit the ED with their acute complaints
- Hosting chemotherapy-specific education programs so patients can better understand and address specific symptoms as they emerge during treatment
- Providing Web and mobile tools that provide 24/7 information and access to appropriate clinical insight

Deploy End-of-Life and Supportive Care Programs

Oncology practices have traditionally struggled when it comes to care delivered in the last weeks of life. While on one hand supportive care does not extend to enough people, the rising costs of healthcare have also transferred a substantial burden to patients, families, and the healthcare system at the end of life. Poor comprehension of the reality of care options, especially when further efforts are fruitless, prolongs suffering, discomfort, and distress for patients and families while incurring substantial cost without the hope for a positive outcome. However, the momentum behind value-based care models is compelling practices to review care management at the end of life and incorporate new approaches.

An emerging group of OCM practices are taking the stance that families deserve a full exploration of care options at the end of life in concert with some payers going so far as to promote full disclosure. Unfortunately, with the ongoing proliferation of the internet, patients and families sometimes interpret advertising as an appropriate source of clinical data and pressure oncologists to provide such care nonetheless. However, study results indicate that care provided under these circumstances is not only not helpful to patients and families, but can harm them. A study published July 23, 2015 in *JAMA Oncology*,[4] found that among the patients who were generally healthy and active at the start of the study, palliative chemotherapy use was associated with worse quality of life in their last week of life and showed no benefit to overall survival. Those who were less healthy at the study's outset experienced no net effect from the treatment, both in quality of life and survival.

What are leading practices doing to address these complex challenges? They are taking approaches that include:

1. Instituting aggressive advance care programs early in the disease trajectory, leveraging counselors
2. Introducing palliative and supportive care programs that can evolve into end-of-life activities as needed
3. Leveraging their care management and navigation capabilities to see appropriate patients through the final stages of their disease. These approaches have been validated by results from similar efforts established among payers, such as Aetna's Compassionate Care Program.[3]

Conclusion

Value-based care is a vision for advancing the Triple Aim that has united stakeholders across the healthcare spectrum, without an equally aligned road map for fulfilling its promise. However, a core group of OCM practices has begun to forge a path with our company, Integra Connect, that places a laser focus on the top cost drivers; directly targets those drivers with focused, high-impact interventions; and ingrains those interventions into the core daily workflows of the practice as well as the composition and focus of care teams. To optimize efficiency, they enable those workflows with new technologies that aggregate disparate sources of data into a holistic patient view that supports their transition to whole person care while simultaneously realizing cost and quality targets for ongoing financial and clinical success. ◆

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FUNDING SOURCE

Integra Connect

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Lending the Patient Voice to Oncology Quality Measurement

Surabhi Dangi-Garimella, PhD

ALTHOUGH VALUE-BASED HEALTHCARE is not a new phenomenon, "We are coming to grips with the patient being a key part of the system," said Ronald Walters, MD, MBA, MHA, MS, associate vice president of medical operations and informatics at The University of Texas MD Anderson Cancer Center. Walters appeared at the National Comprehensive Cancer Network (NCCN)'s Oncology Policy Summit on Redefining Quality Measurement in Oncology, held September 25 in Washington, DC.

WALTERS

Walters said that initially, quality measures associated with reimbursement were primarily provider-centric. More recently, there has been a shift, placing the patient at the center of care and reimbursement,

"Why aren't these measurements a key part of the health system yet?" Walters asked. He believes it is even more important to include measurements that are geared toward those who are not patients yet, meaning an emphasis on preventive care, and listed a set of provider-centric measures of value, which include training, education, certification, volume, and processes of care.

"We know there is a definite relation between volume and patient outcomes," Walters said, adding that over time, a physician's experience and training play a significant role in determining outcomes. However, he warned that the provider-centric value equation can fail.

"Do care providers talk to each other? Large integrated healthcare systems do a very good job with this…but huge gaps exist in the community care setting."

—Ronald Walters, MD, MBA, MHA, MS,
The University of Texas MD Anderson Cancer Center

According to Walters, the most important quality measure for systems of care include cost, resource utilization (both over- and underutilization), site of care and supportive information, and care coordination:

Cost. He emphasized that despite mixed opinions, cost is a real quality measure because inefficiencies in a healthcare system can prove costly. "When you are the patient, price is not an issue when it comes to your [own] health," Walters said. However, inefficient care delivery can significantly impact the health system's bottom line.

Resource utilization. Addressing the fact that there have been questions around whether managed care improves patient outcomes, Walters cited his personal experiences in the clinic around the use of positron emission tomography (PET) scans in patients with breast cancer. He said some patients demand a PET scan because a friend had good outcomes when managing the disease. Citing NCCN guidelines on PET scans and their routine use in the clinic—which do not recommend a PET scan for noninvasive stage I, II, or operable II breast cancer for staging—Walters asked, "How can we handle that normality equation?" so patients are assured they are doing well without unnecessary scans.

Site of care. Walters explained that outcomes vary based on patient access to specific treatments and services. It is vital, he said, that a patient has access to all of the providers that are necessary to ensure the best outcomes. "This will increasingly be a measure for an individual person or patient," he predicted.

© MONKEY BUSINESS

As part of its focus on quality, the National Comprehensive Cancer Network is developing outcomes measures that focus on patient preferences and values.

Care coordination. "Do care providers talk to each other?" Walters asked, highlighting the importance of systems of information transfer to allow seamless exchange of patient information. "Large integrated healthcare systems do a very good job with this…but huge gaps exist in the community care setting," he said.

He then shifted attention toward patient-centric measures of value, which include patient preferences and values, experience (including satisfaction), engagement, and outcomes. "Often, what's entered in our system is the provider's interpretation of the patient's status," Walters said. To overcome this gap, technology platforms are being developed that can capture patient feelings, he said. However, this is not an easy task, Walters added, explaining that "it takes time; it requires an active discussion [between the patient and the provider] and active listening."

Outcomes measures that focus on the patient's preferences and values have a few key requirements:

- Better integrated data systems
- Multi-system analytics
- Data transparency
- System attribution and accountability of outcomes
- Recognition of the fluid nature of measures over time.

NCCN is actively working on this, Walters said, with a focus on the entire spectrum of the care continuum and active representation of the patient perspective on the committee that is developing these measures. ◆

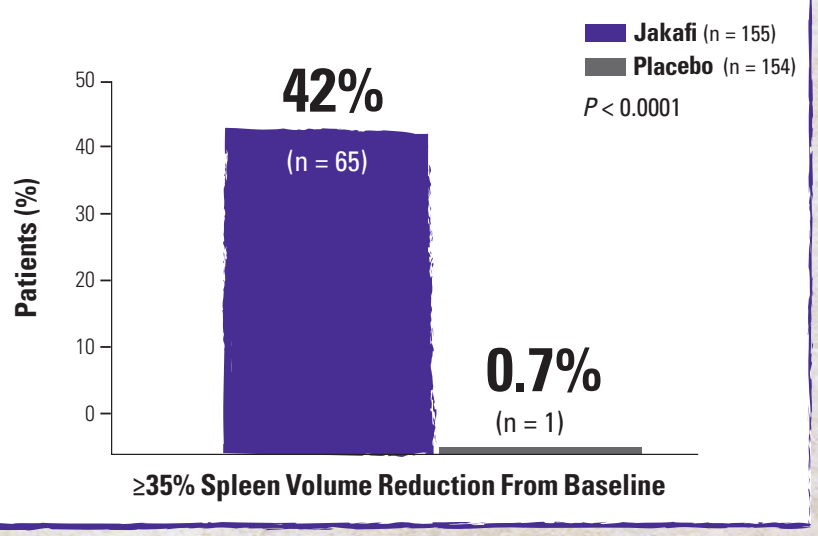
Provide your members with the option that's

FDA APPROVED FOR INTERMEDIATE OR HIGH-RISK MYELOFIBROSIS

In COMFORT-I* and COMFORT-II,† Jakafi® (ruxolitinib) significantly reduced spleen volume compared with patients receiving placebo or best available therapy, respectively[1-3‡]

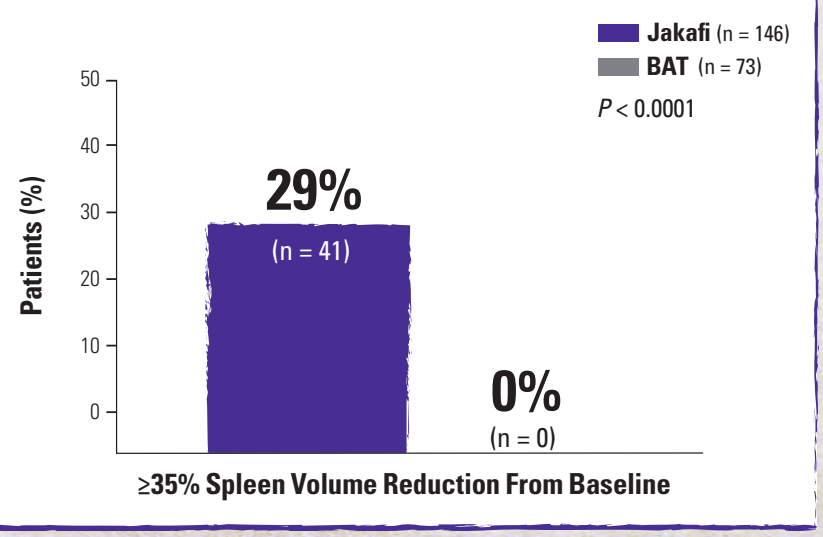
- The primary end point was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline at week 24 as measured by CT or MRI[1,2]

COMFORT-I Primary End Point: Spleen Volume Reduction at Week 24[1,2]



- The primary end point was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline at week 48[1,3]

COMFORT-II Primary End Point: Spleen Volume Reduction at Week 48[1,3]



BAT, best available therapy.

* COMFORT-I (COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment-I) was a randomized, double-blind, placebo-controlled phase 3 study with 309 patients with intermediate-2–risk or high-risk myelofibrosis.[1,2]

† COMFORT-II (COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment-II) was a randomized, open-label phase 3 study with 219 patients with intermediate-2–risk or high-risk myelofibrosis.[1,3]

‡ Best available therapy in COMFORT-II included hydroxyurea (46.6%) and glucocorticoids (16.4%), as well as no medication, anagrelide, epoetin alfa, thalidomide, lenalidomide, mercaptopurine, thioguanine, danazol, peginterferon alfa-2a, interferon-α, melphalan, acetylsalicylic acid, cytarabine, and colchicine.[4]

Important Safety Information

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC $<0.5 \times 10^9$/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines

Jakafi® ruxolitinib (tablets)

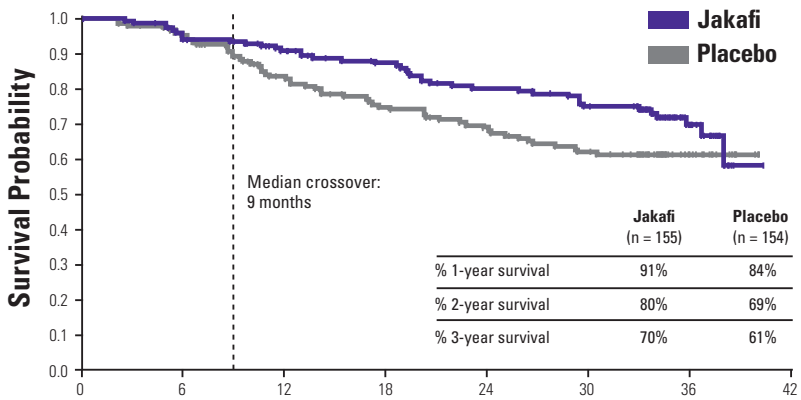
Indications and Usage

Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post–polycythemia vera myelofibrosis and post–essential thrombocythemia myelofibrosis.

Overall survival was a prespecified secondary end point in COMFORT-I and COMFORT-II[1]

- COMFORT-I: At 3 years, survival probability was 70% for patients originally randomized to Jakafi and 61% for those originally randomized to placebo[1]
- COMFORT-II: At 3 years, survival probability was 79% for patients originally randomized to best available therapy[1]

COMFORT-I Overall Survival: Kaplan-Meier Curves by Treatment Group[1]

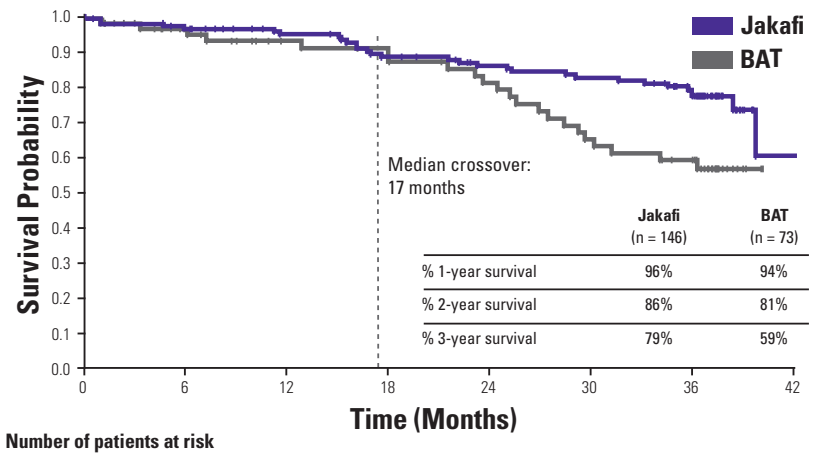


	Jakafi (n = 155)	Placebo (n = 154)
% 1-year survival	91%	84%
% 2-year survival	80%	69%
% 3-year survival	70%	61%

Number of patients at risk

Jakafi	155	145	134	122	111	102	29	0
Placebo	154	142	117	101	92	82	32	0

COMFORT-II Overall Survival: Kaplan-Meier Curves by Treatment Group[1]



	Jakafi (n = 146)	BAT (n = 73)
% 1-year survival	96%	94%
% 2-year survival	86%	81%
% 3-year survival	79%	59%

Number of patients at risk

Jakafi	146	135	126	115	107	104	33	0
BAT	73	58	50	47	42	33	9	0

BAT, best available therapy.

- Because of progression-driven events or at the physician's discretion, patients randomized to placebo (COMFORT-I) or best available therapy (COMFORT-II) who crossed over to receive Jakafi continued to be grouped within their original randomized assignment for analysis purposes[4]
- All patients in the placebo group either crossed over or discontinued[1]

- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation
- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- The three most frequent non-hematologic adverse reactions (incidence >10%) were bruising, dizziness and headache
- A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breast-feed

Please see Brief Summary of Full Prescribing Information for Jakafi on the following pages.

To learn more about Jakafi, visit **Jakafi.com/HCP**.

References: 1. Jakafi Prescribing Information. Wilmington, DE: Incyte Corporation. **2.** Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med*. 2012;366(9):799-807. **3.** Harrison C, Kiladjian J-J, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012;366(9):787-798. **4.** Data on file. Incyte Corporation. Wilmington, DE.

Jakafi®
ruxolitinib (tablets)

BRIEF SUMMARY: For Full Prescribing Information, see package insert.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [*see Dosage and Administration (2.1) in Full Prescribing Information*]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [*see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 X 10^9/L) was generally reversible by withholding Jakafi until recovery [*see Adverse Reactions (6.1) in Full Prescribing Information*]. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. [*see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*]. **Risk of Infection** Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. *Tuberculosis* Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. *PML* Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate. *Herpes Zoster* Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [*see Adverse Reactions (6.1) in Full Prescribing Information*]. *Hepatitis B* Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. **Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi** Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with myelofibrosis have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [*see Dosage and Administration (2.5) in Full Prescribing Information*], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. **Non-Melanoma Skin Cancer** Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. **Lipid Elevations** Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

ADVERSE REACTIONS The following serious adverse reactions are discussed in greater detail in other sections of the labeling: • Thrombocytopenia, Anemia and Neutropenia [*see Warnings and Precautions (5.1) in Full Prescribing Information*] • Risk of Infection [*see Warnings and Precautions (5.2) in Full Prescribing Information*] • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [*see Warnings and Precautions (5.3) in Full Prescribing Information*] • Non-Melanoma Skin Cancer [*see Warnings and Precautions (5.4) in Full Prescribing Information*]. 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. **Clinical Trials Experience in Myelofibrosis** The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with myelofibrosis in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 X 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 X 10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse drug reactions were thrombocytopenia and anemia [*see Table 2*]. Thrombocytopenia, anemia and neutropenia are dose related effects. The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache [*see Table 1*]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 1: Myelofibrosis: Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

	Jakafi (N=155)			Placebo (N=151)		
Adverse Reactions	**All Grades[a] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Bruising[b]	23	<1	0	15	0	0
Dizziness[c]	18	<1	0	7	0	0
Headache	15	0	0	5	0	0
Urinary Tract Infections[d]	9	0	0	5	<1	<1
Weight Gain[e]	7	<1	0	1	<1	0
Flatulence	5	0	0	<1	0	0
Herpes Zoster[f]	2	0	0	<1	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes contusion, ecchymosis, hematoma, injection site hematoma, periorbital hematoma, vessel puncture site hematoma, increased tendency to bruise, petechiae, purpura
[c] includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthitis
[d] includes urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, nitrite urine present
[e] includes weight increased, abnormal weight gain
[f] includes herpes zoster and post-herpetic neuralgia

Description of Selected Adverse Drug Reactions **Anemia** In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (<1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients. **Thrombocytopenia** In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50 X 10^9/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in <1% of patients receiving Jakafi and <1% of patients receiving control regimens. Patients with a platelet count of 100 X 10^9/L to 200 X 10^9/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 X 10^9/L (17% versus 7%). **Neutropenia** In the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study[a]

	Jakafi (N=155)			Placebo (N=151)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Thrombocytopenia	70	9	4	31	1	0
Anemia	96	34	11	87	16	3
Neutropenia	19	5	2	4	<1	1

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Additional Data from the Placebo-controlled Study 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was <1% for Jakafi with no Grade 3 or 4 AST elevations. 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations. **Clinical Trial Experience in Polycythemia Vera** In a randomized, open-label, active-controlled study, 110 patients with polycythemia vera resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy [*see Clinical Studies (14.2) in Full Prescribing Information*]. The most frequent adverse drug reaction was anemia. Table 3 presents the most frequent non-hematologic treatment emergent adverse events occurring up to Week 32. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi.

Table 3: Polycythemia Vera: Treatment Emergent Adverse Events Occurring in ≥ 6% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

	Jakafi (N=110)		Best Available Therapy (N=111)	
Adverse Events	**All Grades[a] (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Headache	16	<1	19	<1
Abdominal Pain[b]	15	<1	15	<1
Diarrhea	15	0	7	<1
Dizziness[c]	15	0	13	0
Fatigue	15	0	15	3
Pruritus	14	<1	23	4
Dyspnea[d]	13	3	4	0
Muscle Spasms	12	<1	5	0
Nasopharyngitis	9	0	8	0
Constipation	8	0	3	0
Cough	8	0	5	0
Edema[e]	8	0	7	0
Arthralgia	7	0	6	<1
Asthenia	7	0	11	2
Epistaxis	6	0	3	0
Herpes Zoster[f]	6	<1	0	0
Nausea	6	0	4	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes abdominal pain, abdominal pain lower, and abdominal pain upper
[c] includes dizziness and vertigo
[d] includes dyspnea and dyspnea exertional
[e] includes edema and peripheral edema
[f] includes herpes zoster and post-herpetic neuralgia

Other clinically important treatment emergent adverse events observed in less than 6% of patients treated with Jakafi were: Weight gain, hypertension, and urinary tract infections. Clinically relevant laboratory abnormalities are shown in Table 4.

Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment[a]

	Jakafi (N=110)			Best Available Therapy (N=111)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Hematology						
Anemia	72	<1	<1	58	0	0
Thrombocytopenia	27	5	<1	24	3	<1
Neutropenia	3	0	<1	10	<1	0
Chemistry						
Hypercholesterolemia	35	0	0	8	0	0
Elevated ALT	25	<1	0	16	0	0
Elevated AST	23	0	0	23	<1	0
Hypertriglyceridemia	15	0	0	13	0	0

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

DRUG INTERACTIONS Drugs That Inhibit or Induce Cytochrome P450 Enzymes Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9. **CYP3A4 inhibitors:** The C_{max} and AUC of ruxolitinib increased 33% and 91%, respectively following concomitant administration with the strong CYP3A4 inhibitor ketoconazole in healthy subjects. Concomitant administration with mild or moderate CYP3A4 inhibitors did not result in an exposure change requiring intervention [*see Pharmacokinetics (12.3) in Full Prescribing Information*]. When administering Jakafi with strong CYP3A4 inhibitors, consider dose reduction [*see Dosage and Administration (2.3) in Full Prescribing Information*]. **Fluconazole:** The AUC of ruxolitinib is predicted to increase by approximately 100% to 300% following concomitant administration with the combined CYP3A4 and CYP2C9 inhibitor fluconazole at doses of 100 mg to 400 mg once daily, respectively [*see Pharmacokinetics (12.3) in Full Prescribing Information*]. Avoid the concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily [*see Dosage and Administration (2.3) in Full Prescribing Information*]. **CYP3A4 inducers:** The C_{max} and AUC of ruxolitinib decreased 32% and 61%, respectively, following concomitant administration with the strong CYP3A4 inducer rifampin in healthy subjects. No dose adjustment is recommended; however, monitor patients frequently and adjust the Jakafi dose based on safety and efficacy [*see Pharmacokinetics (12.3) in Full Prescribing Information*].

USE IN SPECIFIC POPULATIONS Pregnancy Pregnancy Category C: *Risk Summary* There are no adequate and well-controlled studies of Jakafi in pregnant women. In embryofetal toxicity studies, treatment with ruxolitinib resulted in an increase in late resorptions and reduced fetal weights at maternally toxic doses. Jakafi should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Animal Data* Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There was no evidence of teratogenicity. However, decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). **Nursing Mothers** It is not known whether ruxolitinib is excreted in human milk. Ruxolitinib and/or its metabolites were excreted in the milk of lactating rats with a concentration that was 13-fold the maternal plasma. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Jakafi, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** The safety and effectiveness of Jakafi in pediatric patients have not been established. **Geriatric Use** Of the total number of patients with myelofibrosis in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. **Renal Impairment** The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects [CrCl 72-164 mL/min (N=8)] and in subjects with mild [CrCl 53-83 mL/min (N=8)], moderate [CrCl 38-57 mL/min (N=8)], or severe renal impairment [CrCl 15-51 mL/min (N=8)]. Eight (8) additional subjects with end stage renal disease requiring hemodialysis were also enrolled. The pharmacokinetics of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function. However, plasma AUC values of ruxolitinib metabolites increased with increasing severity of renal impairment. This was most marked in the subjects with end stage renal disease requiring hemodialysis. The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in metabolite exposure. Ruxolitinib is not removed by dialysis; however, the removal of some active metabolites by dialysis cannot be ruled out. When administering Jakafi to patients with myelofibrosis and moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min) with a platelet count between 50 X 10^9/L and 150 X 10^9/L, a dose reduction is recommended. A dose reduction is also recommended for patients with polycythemia vera and moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min). In all patients with end stage renal disease on dialysis, a dose reduction is recommended [*see Dosage and Administration (2.4) in Full Prescribing Information*]. **Hepatic Impairment** The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects (N=8) and in subjects with mild [Child-Pugh A (N=8)], moderate [Child-Pugh B (N=8)], or severe hepatic impairment [Child-Pugh C (N=8)]. The mean AUC for ruxolitinib was increased by 87%, 28% and 65%, respectively, in patients with mild, moderate and severe hepatic impairment compared to patients with normal hepatic function. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1-5.0 hours versus 2.8 hours). The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in ruxolitinib exposure except in the severe (Child-Pugh C) hepatic impairment cohort where the pharmacodynamic activity was more prolonged in some subjects than expected based on plasma concentrations of ruxolitinib. When administering Jakafi to patients with myelofibrosis and any degree of hepatic impairment and with a platelet count between 50 X 10^9/L and 150 X 10^9/L, a dose reduction is recommended. A dose reduction is also recommended for patients with polycythemia vera and hepatic impairment [*see Dosage and Administration (2.4) in Full Prescribing Information*].

OVERDOSAGE There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of ruxolitinib.

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Navigating the Quality Landscape in Oncology: Pitfalls and Lessons Learned

Surabhi Dangi-Garimella, PhD

ENSURING ACCESS TO APPROPRIATE data and using that information to improve healthcare outcomes remains an ongoing challenge. This was the conclusion drawn by panelists participating at the National Comprehensive Cancer Network's Oncology Policy Summit on Redefining Quality Measurement in Oncology, held September 25 in Washington, DC.


SPANGLER


GRIGGS


FOX


FACKTOR


GOODMAN

The biggest challenge, the panelists said, involved gathering cutting-edge data. "We have limited access to data," said Andrew York, PharmD, JD, CMS. While CMS has created a registry of what it considers high-quality data, "Feasibility is hard, and it's also hard for us to implement changes." There are practical and operational challenges.

Ronald Walters, MD, MBA, MHA, MS, The University of Texas MD Anderson Cancer Center, added that the growth of personalized medicine will make the process even more challenging. "Cross-cutting measures don't have strong evidence," said Jason Spangler, MD, MPH, Amgen. Citing the Oncology Care Model (OCM), he said that clinically specific measures provide more information compared with cross-cutting measures, which are usually outcomes measures.

According to Mary Lou Smith, JD, MBA, of the Research Advocacy Network, the dearth of a high number of enrollees in adult clinical trials is another issue. "With a 5% adult trial enrollment rate, using real-world evidence to inform drug development is a challenge," she said.

Physician buy-in, especially when documenting information around things like pain and hospice/palliation is important, according to Jennifer Griggs, MD, MPH, University of Michigan, as is care coordination. "However, it is important to define exactly what needs to be coordinated," she said.

Spangler highlighted the importance of shared decision making and patient–provider conversation, especially when a patient is receiving precision medicine. "With precision care, patients need to know that quality measurements around their precision treatment may be unique," he said, explaining the likelihood of a disconnect between standard quality metrics and those used for a patient undergoing precision treatment.

Introducing patient-centricity to the discussion, John Fox, MD, MS, Priority Health, said, "We don't just have to measure everything, but we do need to understand the accuracy of what we are measuring. We definitely need a quality measure to understand patients' comprehension of their treatment and disease."

Matthew Alan Facktor, MD, Geisinger Health, Commission on Cancer, alluded to the fact that most quality metrics in use today are process measures, which he said creates a significant gap in quality measurement. He emphasized the need to pay greater attention to structural measures, such as site of care; availability of tools to deliver quality care; and patient-reported outcomes measures.

When the moderator, Clifford Goodman, PhD, The Lewin Group, asked whether CMS has been thinking about these specific measures, York said that the Center for Medicare & Medicaid Innovation started looking at outcomes measures, but the requirement was for infrastructure changes to ensure ramping up of quality-based programs.

"Our measures were closest to outcomes measures," York said, adding that although they were process measures, they were geared to collect healthcare utilization metrics. Citing an example of pain as an outcomes measure, he said "We need to include a process measure to ensure [pain medication] is being administered."

When asked if the existing quality measurement apparatus is suitable for quantifying patient experiences with quality of their treatment, Walters replied in the negative.

Griggs narrated her experience at Michigan with patient interaction: measuring anxiety, stress, and non–cancer-related issues. "The 17 measures that evolved following their patient interaction lined up well with ASCO [American Society of Clinical Oncology]'s measures submitted under the Merit-based Incentive Payment System." While these measures have been identified, operationalizing them, is the next step, she said.

"We don't just have to measure everything, but we do need to understand the accuracy of what we are measuring. We definitely need a quality measure to understand patients' comprehension of their treatment and disease."

—John Fox, MD, MS, Priority Health

"We can actually collect data on switching doctors and the chemotherapy administered in the last 14 days of care…that could be incorporated as a quality measure," Walters said.

Smith says she believes that care coordination soon will be included as a quality measure and that precision medicine will help this. Health plans have already been thinking about this. "We have a care management fee in our oncology home model, which is equivalent to the MEOS [monthly enhanced oncology service] payment," under OCM, which helps ensure care coordination receives monetary support.

"We have the medical oncologist targeted as our care coordinator," York explained, because often the primary care providers aren't ready to take up that responsibility. He explained, however, that care navigation can be spread across the practice to include the nurse navigator, the front office administrator, and the oncologist.

When asked about dealing with patients who are dissatisfied when they do not receive the treatment they seek because it may not be supported by evidence, Walters explained that it may not affect quality measurement because "many measures have denominator exclusions that includes documentation on why the patient was refused."

Explaining the industry's struggle with sharing real-world evidence that supports the value proposition of their product, Spangler said, "We have limitations on how much of the real-world evidence that we gather can be shared with other stakeholders." This evidence, he suggested, can definitely be included in the development of quality measures.

"We need a parsimonious tight set of meaningful measures that can be used by both health systems and patients," said Griggs.

"Collective accountability is vital: everyone needs to work together to improve the quality of care," added Spangler. ◆

Stakeholders Weigh in on Payment Reform in Cancer Care

Surabhi Dangi-Garimella, PhD

WHEN THE ONCOLOGY CARE MODEL (OCM) program was announced by CMS in early 2016, 196 practices and 17 payers signed on to participate for its 5-year duration. Per the CMS website,[1] the numbers now stand at 190 and 14, respectively. Tuple Health, a healthcare technology start-up, interviewed some of the stakeholders participating in value-based care delivery and the OCM to gain their perspectives of the state of cancer care and healthcare reform. The results were presented Basit Chaudhry, MD, PhD, co-founder and CEO of Tuple Health, and Celeste Roschuni, PhD, user researcher, Tuple Health, at the Community Oncology Alliance Payer Exchange Summit on Oncology Payment Reform, held October 23-24 in Tysons Corner, Virginia.

CHAUDHRY

ROSCHUNI

"Our focus, with these interviews, was on practice variability, stakeholder perception of value/risk, and the transformation process, Roschuni said.

Considerations for practice variation included factors such as the practice size and scope, geography, and patient population, all of which influence structural capacity of a practice, according to Roschuni. The biggest influencer, they found, was a practice's previous experience in delivering value-based care.

Roschuni pointed out that prior experience is more important than practice size. "The general sense is that the OCM design is meant for larger, more advanced practices. But each practice has its own struggles, and there's really no average OCM practice," she emphasized.

Tuple Health categorized the surveyed OCM-participating practices into 4 types, with their qualitative performance predicted based on their experiences:

- **The dubious participant.** These practices decided to participate in the OCM based on hearsay, Roschuni explained, and they "picked the OCM over MIPS," the Merit-based Incentive Payment System that is the less advanced option under the Medicare Access and CHIP Reauthorization Act. These practices, the survey found, are technically still functioning within a fee-for-service mindset and are struggling with value-based care. However, they do appreciate the enhanced patient care that resulted from OCM implementation.
- **The reluctant participant.** These practices participated in the OCM because they may have 1 value-based care champion on their team. They have little or no previous experience with value-based care. Implementing value-based care has required a lot more effort from these practices, including dedicating a person to lead the effort, along with the need for persons to do the reporting.
- **High-expectations participant.** These practices have some experience delivering value-based care, including multipayer demonstration projects and the Oncology Medical Home. They carry a sense of high perceived self-efficacy. Their expectation with the OCM was that it would help them expand further into value-based payment and practice transformation.
- **The pathway participant.** These practices are very focused on improving the patient experience and have previous experience with value-based care delivery. Their prior experience is helping them pull payers into value-based discussions and contracts, and their flexible approach has helped them shift mindsets.

Perceptions of Value and Risk

The survey found a wide variation in value perceptions:
For community practices, value is perceived as quick, convenient, low-cost quality care. "These practices tend to tie risk to things 'beyond their control,' such as drug cost," Roschuni said.

For patients, the location of their site of service is important, as are care coordination and physician competence. For payers, total cost savings based on the site of service is extremely valuable, but within the sphere of the cost of inflation and drug costs, Roschuni said. For the pharmaceutical industry, innovation holds immense value.

The survey found surprising similarity in stakeholder perception of risk. "Risk is compounded by cost inflation within the pharmaceutical industry," Roschuni explained. An example of this is that practices are holding their oncologists responsible for the total cost of patient care, which includes drug costs.

"Another risk is of adverse patient selection because payers have not yet developed robust risk-adjustment methods for their payment models," Roschuni added.

Transformation

Speaking to stakeholder transformation to adapt to the world of value-based care, Roschuni highlighted the fact that it requires a spectrum of activities, including internal transformation, extending practice influence, and expanding payer programs—it cannot be a single event. A major learning from the survey was the importance of physician buy-in—a fact that was reiterated by several participants at this year's meeting.

"Extending a practice's influence requires network development and an expanded scope of the practice's service," Roschuni said, adding that practices often find it easier to expand their network and develop partnerships with other healthcare delivery clinics. However, neither expanded scope of service nor network expansion are accounted for under the current iteration of the OCM, Roschuni concluded. ◆

Dr Lucio Gordan: How Practices and Payers Work Together to Implement OCM

THE IMPLEMENTATION OF THE ONCOLOGY CARE MODEL (OCM) has brought profound culture changes to how oncologists take care of practices and how they operate practices, explained Lucio Gordan, MD, of Florida Cancer Specialists.

How do practices and payers work together to implement OCM?
OCM has brought a very profound change to oncology practice in the country. One hundred ninety practices are participating in OCM these days, and we have to go through culture changes as to how we take care of patients, operational changes, revenue cycle changes, communication changes as to how the operating team communicates with the providers, the physicians, nurse practitioners, etc. It has certainly been a very profound, interesting, rewarding, and with many challenges ahead still, experience for all of us at Florida Cancer Specialists. So, how we did it. Obviously, there was a process of educating the staff, educating the physicians. We are a large practice in Florida. We have about 100-plus offices, almost 400 providers, so we had to do webinars to discuss oncology care model, we got physicians involved via e-mail, Q-and-A, all those things to make it happen. So, it was a very laborious process that continues to be active and we perfect every time. ◆

REFERENCE

Oncology Care Model. CMS website. innovation.cms.gov/initiatives/oncology-care/. Updated October 5, 2017. Accessed October 25, 2017.

The Commercial Payer OCM Experience: Year 1

Surabhi Dangi-Garimella, PhD

IN 2016, THE CENTER FOR MEDICARE & Medicaid Innovation (CMMI) floated the idea of the Oncology Care Model (OCM) in 2016, it allowed commercial payers the option of participating in this pilot reimbursement and care delivery model. Multipayer participation was an added incentive for provider practices to consider pilot enrollment. Seventeen payers signed up to participate.


ARAN


FRICK


GAMBLE


McCORMICK

At the Community Oncology Alliance (COA)'s Payer Exchange Summit on Oncology Payment Reform, held October 23-24 in Tysons Corner, Virginia, representatives from 3 commercial payer organizations that volunteered to follow CMMI's lead to partner with providers on the OCM took the stage. Panelists Peter Aran, MD, Blue Cross Blue Shield of Oklahoma (BCBSOK); Rene Frick, Blue Cross Blue Shield of South Carolina (BCBSSC); and Liz McCormick, Priority Health, took the stage to speak with COA's Bo Gamble.

First, Gamble asked the panelists to provide an overview of their primary focus with the OCM.

Frick said that BCBSSC has placed emphasis on monthly care management, shared savings, and upside-only risk in the first year. "We are focused on only the first 3 claims-based OCM measures," she said, which they will analyze for the practices. In addition, there's regular communication with the practices, in the form of quarterly face-to-face meetings, for data review. She also said that with this pilot, BCBSSC is focusing on 3 cancer types.

BCBSOK is still working out details, but will cover between 4 and 6 cancer types, Aran told the audience. In an effort to curb reporting requirements on providers, its focus is on 5 quality measures, which will piggy-back on OCM measures. "We want to make the data reporting as less-burdensome for the practices as possible," he said.

Aran cited the experience with the patient-centered medical home model, which he described as "a concept that never took off because early adopters did not have the money to build the infrastructure to bring about required changes." He explained that CMS realized the need to infuse this money up front so practices could implement necessary changes, such as care navigators or changes with the workflow.

McCormick pointed out the importance of the Monthly Enhanced Oncology Service payment, adding that Priorty Health also is limiting physician reporting to 3 quality metrics, in addition to a depression screening measure and the 13-point Institute of Medicine Care Management Plan. Highlighting the difference in the scope of the different programs that Priority Health is participating in, McCormick said, "We are a part of CPC [Comprehensive Primary Care]. In the oncology space, we have 5 practices with about 2300 members; CPC+ includes 40 practices with 250,000 members."

She added that they have restricted shared savings only for practices with 200 or more patients, which means only 1 of their existing provider groups qualifies. "The focus is on in-patient utilization and [emergency department] visits."

Comparing their participation in the Oncology Medical Home, prior to the OCM, McCormick said that a big difference has been data mining. "We'd like to have a dedicated data analyst to bring more story-telling to our health plan," she said, adding that understanding the key impact of the reimbursement model on the plan is important.

Aran said that while collaboration is key, transformation is equally important. He explained that the clinical transformation is not a stand-alone; payers, the pharmaceutical industry, and technology platform vendors are undergoing transformation, as well. "Keep coming back to us even if we seem uncooperative, with programs that make sense, and we will be cooperative," Aran added.

A major point of contention within the OCM has been the discussion around sharing downside risk between payers and providers. Aran said that a majority of physicians were trained to define risk only in clinical terms, meaning the clinical risk that patients face due to their disease and treatment. "For physicians, it's hard to think of this risk in terms of business. However, we, as payers, want more buy-in from physicians," he added.

> **"Keep coming back to us even if we seem uncooperative, with programs that make sense, and we will be cooperative."**
>
> —Peter Aran, MD, Blue Cross Blue Shield of Oklahoma

Priority Health does not risk adjust. "We have contractual addendums, and there are some 2-sided risks in these contracts, but not in the context of the OCM," McCormick said.

With BCBSSC, 2-sided risk falls under the accountable care organization (ACO) program. "OCM practices that are within those ACOs will eventually migrate to 2-sided risk," she said, adding that only 2 or 3 of their practices that are comfortable with the 2-sided risk would be migrating over.

Aran reminded the audience that the center of the universe needs to be the patient, patients' families, and lay caregivers. "Come with a plan for care delivery reform, not just bending the cost curve," he said.

Frick agreed, adding that cost reduction should not mean deficit of quality. "Quality deficit means physicians would lose their part of the shared savings…and we will revisit the model to look for ways to improve." ◆

Dr Jeff Patton Highlights Challenges Encountered With Implementing OCM

IMPLEMENTING THE ONCOLOGY CARE MODEL (OCM) has presented several challenges, such as manually submitting data, keeping up with status of therapy, and billing, said Jeff Patton, MD, CEO of Tennessee Oncology.

What challenges has your practice encountered with implementing OCM?
Reporting is very difficult, for us it's basically manual. We just submitted our data and it took [full-time employees] 6 months to abstract the data, so that's a challenge. Just keeping up with when folks are on therapy, off, when they go on and come off of an episode. Billing for orals is a challenge because sometimes those are filled elsewhere so we don't know what the fill date is, and so how do you fill out a fill date when you don't know?

I think another big challenge is with novel therapies. We do a lot of clinical research so our doctors tend to adopt new technology, new therapies quicker, and in this program apparently that's a bad thing. We think it's a good thing, but we think we're getting penalized for that. And then last, the lack of having real-time data feedback on both quality measures and on the financial impact. You know, 18 months is a long time to wait for feedback. ◆

Will 2-Sided Risk Be a Reality in the OCM?

Kelly Davio

THE ONCOLOGY CARE MODEL (OCM), a pilot reimbursement program developed by CMS' Center for Medicare & Medicaid Innovation (CMMI), is now in its second year. To discuss the learnings and how the program can change, 3 provider representatives from across the country sat on a panel with representatives from CMMI at the Community Oncology Alliance's Payer Exchange Summit on Oncology Payment Reform, held October 23-24 in Tysons Corner, Virginia. The discussion touched on incentivizing physicians to accept 2-sided risk, the ability to engage additional payers, and the future of oncology bundle payments.

Moderated by Lara Strawbridge of CMS, participants included Andy York, PharmD, JD, CMS; Terrill Jordan, Regional Cancer Care Associates (RCCA); Jeff Hunnicutt, Northwest Medical Specialties; and Ahmad Mattour, MD, Henry Ford Health System.

York started the discussion with a presentation on lessons learned in the cancer episode-of-care space. He then provided an overview of the OCM, describing it as a 2-part model designed around episodes of care, with emphasis on:

- 24-hour access to care
- Care navigation
- Treating patients with treatments aligned with national guidelines

The OCM wants physicians to use both certified electronic health records (EHRs) and their data for care quality improvement. The model reviews 6-month episodes of care and allows performance-based payment based on retrospective performance. It's a multipayer model with 17 commercial payers participating, York told the audience. "We need more participation to reach that critical mass of payers."

Past, Present, and Future of the OCM

Although 196 practices initially participated in the OCM, the number is now at 192 following practice consolidations, York said. He highlighted the following major milestones so far:

- Three quarterly feedback reports with claims data have been shared with enrolled practices
- Practices currently have 2 submission periods
- The first round of clinical data submission has occurred
- On schedule to provide the first round of reconciliation in early 2018

York mentioned that the short-term change that CMS is working toward is to reduce the reporting burden by working with EHR vendors and stakeholders. Acknowledging that "it's been a moving target," he said that one change has been to move from quarterly to semiannual reporting. The more long-term goals are to refine the OCM bundle by being responsive to program participants.

York recommended an ongoing dialogue between payers—both commercial and CMS—and providers as the model continues to be refined. "For many payer partners, having large enough bundles is a barrier. But it's OK to start with higher-volume, more predictable cancer types," he added. Importantly, all changes to the program should be scalable, and sharing best-practices is a very good way to move forward and improve, he said.

Speaking to the experience at RCCA, Jordan said that they started looking at clinical integration, a holistic model of providing care, not just in office but working with physicians in other offices, prior to the OCM. It made sense for them to "work on a roadmap we didn't have to build ourselves." Being able to work with other like-minded practices was important, according to Jordan.

For the Henry Ford Cancer Center, joining the OCM program "was the right thing to do," said Mattour, adding that the change would provide the means to implement the quality projects they wanted to deliver to patients and achieve a higher level of care. He noted that their previous experience with similar models, such as a CMS project focused on evaluating earlier screening for cancers in specific populations, would provide benefits in terms of cost reduction.

For Hunnicutt's oncology practice, multiyear value-based care programs provided opportunity "to get our feet wet." Identifying the value of patient feedback and providing enhanced services solidified their decision of program participation.

When asked to identify some of the issues with the OCM, Hunnictt said that while "this program has the legs to be successful," there were some issues with the model that they spotted early on, and CMMI was interested in practice feedback.

"Compliance is time consuming and labor intensive," said Mattour. "Identifying OCM-eligible patients is a problem," and he would like to see the list being provided earlier. He too appreciated that CMS was open to practice feedback.

Jordan came back with a different take on the information overload, saying that it "was actually very useful. When you look at the information, there was acknowledgment that flexibility was important, and it is a community effort where everyone wants to help others."

Strawbridge emphasized that payers and providers are all in this together. "We do all share the same goals," she said. "Working to determine best practices for identifying patients who can be included in the OCM is important, but a challenge in the retrospective nature of the model.

Jordan said that variability arises when you have different programs and you don't have everybody on the same page. "We didn't know quite how daunting the reporting would be," but when the practice spoke with payers, they acknowledged that there couldn't be so much variance in reporting. He explained that they are trying to drive all their reporting to reflect OCM requirements to streamline their internal workflow.

Mattour agreed, and said that they too are working with multiple stakeholders, and their hope is that multiple payers will be more engaged with the OCM or a similar program. "We want to do what's best for patients in working for a common goal," he added.

The panelists were then asked to share a key advice for provider practices who would want to get involved in the OCM and with other payers. For Hunnicutt, placing the patient at the center of care is vital, in addition to an open line of communication with payers. Mattour emphasized the importance of geographic variations in the patient population, as well as a good understanding of the nuances of the OCM, which he described as being "a full-time commitment," because it will affect workflow, technical requirements, and personnel requirements. "It will improve outcomes. Keeping patients out of the [emergency department] means everybody wins."

Explaining the diversity of the RCCA practices, Jordan said that with the OCM, "there's an education process. "The uncertainty around programs like this, given the commitment you're asking these practices to make, is massive." If programs disappear, those services will go away, which will not be appreciated by patients or practices. "Start preparing now. No matter how much you prepare, you're not going to be prepared for what's going to happen," Jordan said, drawing a simile to "death by reporting."

Making the OCM Sustainable for Your Practice and the Much-Dreaded 2-Sided Risk

"We have to make a strategic decision to embrace rational care," noted Jordan, which requires strategic decision and payer support. Practices require time to change and "in the first 6 months, nothing was done but figuring out what to do." He emphasized the need for a longer-term commitment beyond the current 5 years.

Mattour would like an assurance that the current measures and steps taken for the OCM will continue to receive support, in addition to interdepartmental collaboration, manpower, and software upgrades. Hunnicutt said that the emphasis on value-based care let their providers implement programs that they had wanted for years. "I can't imagine what we'd do if we took away these patients' programs. We have to be able to provide for those programs."

The physicians were noncommittal when it came to 2-sided risk, saying they "needed more visibility into the data elements before making a jump." Mattour said that 2-sided risk tends to favor CMS. "It's difficult to attribute the reasons for a symptom, and patient populations differ. We need more time and data," he added.

"Chairs cannot move on the deck," Jordan explained. "There's no way to take on risk if there's the chance that CMS might change things." ◆

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

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

IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

Learn more at KYPROLIS-HCP.com

Now With Overall Survival Data

WHEN MULTIPLE MYELOMA RELAPSES,

Don't put your patient's survival at risk

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

KRd AS A TRIPLET THERAPY

8.7-month increase in median PFS[3]

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

7.9-month increase in median OS[1]

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

>3x CR or better[3]

32% (KRd) vs 9% (Rd)

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

Kd AS A DOUBLET THERAPY

9.3-month increase in median PFS[3]

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

7.6-month increase in median OS[2]

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

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

See more OS results at KYPROLIS-HCP.com

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

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

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

IMPORTANT SAFETY INFORMATION

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

Please see additional Important Safety Information on left.

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

Kyprolis™ (carfilzomib) for Injection

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

1. INDICATIONS AND USAGE

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

5. WARNINGS AND PRECAUTIONS

5.1 Cardiac Toxicities

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

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

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

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

5.2 Acute Renal Failure

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

5.3 Tumor Lysis Syndrome

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

5.4 Pulmonary Toxicity

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

5.5 Pulmonary Hypertension

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

5.6 Dyspnea

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

5.7 Hypertension

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

5.8 Venous Thrombosis

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

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

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

5.9 Infusion Reactions

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

5.10 Hemorrhage

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

5.11 Thrombocytopenia

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

5.12 Hepatic Toxicity and Hepatic Failure

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

5.13 Thrombotic Microangiopathy

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

5.14 Posterior Reversible Encephalopathy Syndrome

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

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

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

5.16 Embryo-Fetal Toxicity

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

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

6. ADVERSE REACTIONS

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

6.1 Clinical Trials Experience

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

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

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

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

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

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

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

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

[a] Pneumonia includes pneumonia and bronchopneumonia.

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

[c] Cough includes cough and productive cough.

[d] Dyspnea includes dyspnea and dyspnea exertional.

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

[f] Hypertension includes hypertension, hypertensive crisis.

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

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

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

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

Most Common Adverse Reactions (≥ 10% in the Kd Arm) Occurring in Months 1–6 (20/56 mg/m² Regimen in Combination with Dexamethasone)

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

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

[a] Thrombocytopenia includes platelet count decreased and thrombocytopenia.

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

[c] Dyspnea includes dyspnea and dyspnea exertional.

[d] Cough includes cough and productive cough.

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

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

6.2 Postmarketing Experience

The following additional adverse reactions were reported in the postmarketing experience with Kyprolis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: hemolytic uremic syndrome (HUS), gastrointestinal perforation, pericarditis.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Contraception

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Of 598 patients in clinical studies of Kyprolis monotherapy dosed at 20/27 mg/m² by up to 10-minute infusion, 49% were 65 and over, while 16% were 75 and over. The incidence of serious adverse events was 44% in patients < 65 years of age, 55% in patients 65 to 74 years of age, and 56% in patients ≥ 75 years of age. In a single-arm, multicenter clinical trial of Kyprolis monotherapy dosed at 20/27 mg/m² (N = 266), no overall differences in effectiveness were observed between older and younger patients.

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

Of 463 patients treated with Kyprolis dosed at 20/56 mg/m² by 30-minute infusion in combination with dexamethasone, 52% were 65 and over and 17% were 75 and over. The incidence of serious adverse events was 44% in patients < 65 years of age, 50% in patients 65 to 74 years of age, and 57% in patients ≥ 75 years of age. No overall differences in effectiveness were observed between older and younger patients.

8.6 Hepatic Impairment

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

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

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

8.7 Renal Impairment

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

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

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

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

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

How Has the OCM Evolved? Year 1 Provider Updates

Surabhi Dangi-Garimella, PhD

THE 192 PARTICIPATING PRACTICES in CMS' Oncology Care Model (OCM) have received performance feedback from the Center for Medicare & Medicaid Innovation. What have been the major challenges faced by these practices? Were there surprises or were the 1-year results as anticipated? Participants from 2 oncology community practices, and an oncologist–administrator combination, shared their experience with the attendees at the Community Oncology Alliance's Payer Exchange Summit on Oncology Payment Reform, held October 23-24 in Tysons Corner, Virginia.

CHAUDHRY

The session, moderated by Basit Chaudhry, MD, PhD, Tuple Health, saw participation by Jeff Patton, MD, and Aaron Lyss, MBA, both from Tennessee Oncology, and Lucio Gordan, MD, and Sarah Cevallos, both representing Florida Cancer Specialists & Research Institute. Together they represent 2 of the bigger practices participating in the OCM.

The discussion started with a conversation around the biggest challenges faced by oncology practices, which Cevallos identified as "physician communication and culture change within the practice—having providers understand the new requirements." Explaining that Medicare enrollees constitute 50% of the practice's patients, she noted that her practice needed a big change to ensure all reporting and care delivery requirements were in place within a 90-day time frame.

Patton struck a common chord when he acknowledged that culture change is difficult even when every patient is handled in the same way with respect to care delivery, and it "becomes schizophrenic" when each patient is on a different reimbursement path. This complicated physician on-boarding even more, Cevallos said, as it became challenging to make them understand the different tracks: OCM, fee-for-service (FFS), the Merit-based Incentive Payment System, etc. Gordan added that culture change encompassed the need to recruit additional staff, longer working hours, weekend hours, and keeping patients out of the emergency department (ED), among others.

Adequate data management is just as vital, according to Lyss. "Just tracking the patient through the process is fundamental to participating in this model… and we have made much progress compared with a year ago," he added, pointing to the influence of improved infrastructure and quality reporting changes on his practices' capacity to participate in commercial payer models.

Cost Control Pillars

The panelists identified 4 pillars of ensuring care costs remain within limits:

- Clinical pathways to reduce variability and avoid toxicity
- Upfront triage for symptom management and to reduce ED admissions
- Infusing palliative care services throughout patient care
- Care coordination

At Florida Cancer Specialists & Research Institute, private practice physicians have access to data of patients they have referred to the oncology clinic, which, Gordan explained, has helped ensure patients stay out of the ED. An ideal strategy for physician engagement is seeking insight on the front-end, said Lyss, and it also helps improve program implementation.

Cevallos believes there is an imminent need to streamline the quality reporting requirements. "We will have to draw a line soon because it's just getting too much, managing FFS versus value-based care," she said. Another important point she noted was paying adequate attention to keeping healthcare local. Patton emphasized that it is important to meet practices at their level and to understand the different challenges faced by a single-doctor practice versus a bigger practice with multiple physicians on staff.

"We'd like more interaction with payers," Gordan said, "so we can identify metrics that payers consider important," and to normalize outputs from value-based and other contracts without reinventing the wheel.

"We need payer–provider conversations on ways to keep the total cost of care down," said Patton. ◆

CMS Finalizes Reform to Adjust 340B Payments

Jaime Rosenberg

REFORM IS COMING FOR the 340B program, but reaction is mixed.

On November 1, 2018, CMS finalized the Hospital Outpatient Prospective Payment System (OPPS), which will adjust payments for drugs purchased through the program to the average sales price (ASP) minus 22.5%, a change from the current rate of ASP plus 6%. However, rural sole community hospitals, certain cancer hospitals, and children's hospitals will be exempt from the reductions.

The 340B program requires drug manufacturers participating in the Medicaid Drug Rebate Program to provide a discount to covered safety net health providers. It enables these covered entities to stretch federal resources as far as possible to reach more low-income patients who are uninsured and to provide more comprehensive services. Outpatient prescription drugs, over the counter drugs, and clinic-administered drugs within eligible facilities are covered, but vaccines and inpatient drugs are not. However, the program does not specify or control how hospitals use the money generated from the program.

According to CMS, the rule will help lower the cost of prescription drugs for seniors and other Medicare beneficiaries by reducing the payment rate for certain Medicare Part B drugs purchased through the 340B program. The savings from this will be redistributed equally to hospitals covered under the OPPS. A provision of the OPPS will alleviate some burden rural hospitals face by placing a 2-year moratorium on the direct physician supervision requirements for rural hospitals and critical access hospitals.

The Community Oncology Alliance (COA) commended CMS for the reform, saying it is good for both patients and taxpayers. "COA strongly supports this new policy because it will reduce drug costs for seniors by an estimated $320 million on co-payments for drugs in 2018 alone; help to curb outrageous abuse of the 340B program by some large hospitals; and, hopefully, start to reverse the profit incentives that dismantled our nation's community cancer system," the group said in a statement.[2]

Meanwhile, the nation's leading hospital associations have joined together to sue CMS over the payment cuts. America's Essential Hospitals, the American Hospital Association, and the Association of American Medical Colleges said that they believe CMS has overstepped its authority by cutting the drug payments. Tom Nickels, executive vice president of the American Hospital Association, said the change, "is not based on sound policy and punishes hospitals and patients for participation in a program outside of CMS' jurisdiction."[3]

Similarly, Ted Slafsky, president and CEO, 340B Health, denounced the reform, calling it "a backdoor effort to undermine an important drug discount program."[4]

According to Slafsky, the rule will benefit for-profit cancer clinics who turn away the poor, uninsured, and underinsured. It will not lower the cost of drugs for patients or providers and will not expand access to care.

According to Rena M. Conti, PhD, assistant professor of health policy and economics, University of Chicago, the reform will provide relief in 3 major areas: (1) helping patients facing Medicare requirements for infusions or other specialty therapies, (2) eliminating incentives to earn profits by choosing more expensive drugs, and (3) putting on notice those institutions that were revenue driven at the expense of safety net providers.

"Overall, it provides transparency into the program," said Conti. "First, because hospitals will be required to provide more information and use this revenue to provide care to the community. It also provides more transparency to which drugs are eligible to discount because we haven't really known before. There was no public accounting of that until now."

The changes to the 340B program will begin on January 1, 2018. ◆

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Roche Gets Drug Approvals for First Treatment for a Rare Blood Disorder and NSCLC

AJMC® Staff

ROCHE HAD 2 DRUGS approved by the FDA—one for a rare blood disease and the other for first-line treatment for lung cancer.

Vemurafenib (Zelboraf) is the first FDA-approved drug for Erdheim-Chester disease (ECD), a rare blood disorder. Already approved for the treatment of people with unresectable or metastatic melanoma with the BRAF V600E mutation, the new indication includes patients with ECD who harbor the BRAF V600 mutation. Characterized by an abnormal multiplication of histiocytes, these white blood cells can invade normal tissues and organs.

The drug was approved based on data from the phase 2 VE-BASKET study, which used an innovative clinical trial design that matched a disease's underlying genetic profile to the mechanism of action of the medicine. For the 22 people with ECD, the trial showed a best overall response rate of 54.5%.

"This FDA decision means people living with Erdheim-Chester disease will now, for the first time, have an FDA-approved treatment option," Sandra Horning, MD, Roche's chief medical officer and head of global product development, said in a statement.[1] "We are committed to finding new ways to bring medicines to patients with high unmet need, and we are pleased that this innovative clinical trial helped identify Zelboraf for treatment of this rare disease."

The second drug approved was alectinib (Alecensa) as a first-line treatment for people with anaplastic lymphoma kinase (*ALK*)-positive metastatic non–small cell lung cancer (NSCLC). The FDA approved the drug based on results from the phase 3 ALEX study, which showed the drug reduced the risk of disease worsening or death by 47% compared with crizotinib. Median progression-free survival was 25.7 months for people on alectinib, compared with 10.4 months for those on crizotinib.

Alectinib has been recommended in the National Comprehensive Cancer Network guidelines as a treatment option for first-line *ALK*-positive metastatic NSCLC.

"Our goal is to develop medicines that have the potential to significantly improve upon the standard of care," Horning said in a separate statement.[2] "In our pivotal study, Alecensa significantly extended the time that people lived without their disease worsening compared to crizotinib and also showed a marked reduction in the risk of their cancer spreading to the brain." ◆

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ASCO: Alcohol Linked to Several Types of Cancer

Jaime Rosenberg

ALCOHOL CONSUMPTION, whether light, medium, or heavy, is linked to higher risks of several leading cancers, according to findings released by the American Society of Clinical Oncology (ASCO).[1]

ASCO has listed alcohol as a definite risk factor for cancer, saying that it contributed to 5% to 6% of new cancers and cancer deaths globally. The evidence linked alcohol consumption with breast, colon, esophagus, and head and neck cancers.

"People don't typically associate drinking beer, wine, and hard liquor with increasing their risk of developing cancer in their lifetimes," said ASCO President Bruce Johnson, MD, FASCO, in the statement. "However, the link between increased alcohol consumption and cancer has been firmly established and gives the medical community guidance on how to help their patients reduce their risk of cancer."

According to the National Cancer Opinion Survey conducted by ASCO earlier this year,[2] 70% of Americans do not identify alcohol as a risk factor for cancer, and only 38% are limiting their alcohol intake as a way to reduce the risk of cancer.

In addition to raising awareness of the correlation between alcohol consumption and cancer, ASCO also put emphasis on implementing evidence-based policy recommendations to reduce excessive alcohol consumption:

- Provide alcohol screening and brief interventions in clinical settings
- Regulate alcohol outlet density
- Increase alcohol taxes and prices
- Maintain limits on days and hours of sale
- Enhance enforcement of laws prohibiting sales to minors
- Restrict youth exposure to advertising of alcoholic beverages
- Include alcohol control strategies in comprehensive cancer control plans
- Support efforts to eliminate the use of "pinkwashing" to market alcoholic beverages.

For example, discouraging alcoholic beverage companies from exploiting the color pink or pink ribbons to show a commitment to finding a cure for breast cancer given the evidence that alcohol consumption is linked to an increased risk of breast cancer.

According to ASCO, excessive alcohol consumption can also delay or negatively affect cancer treatment. Oncologists have the ability to identify strategies to help patients reduce their alcohol intake; address racial, ethnic, gender, and sexual orientation disparities that may place these populations at increased cancer risk; and serve as community advisers and leaders to raise awareness of alcohol as a cancer risk behavior.

"ASCO joins a growing number of cancer care and public health organizations in recognizing that even moderate alcohol use can cause cancer," said Noelle K. LoConte, MD, lead author of the statement and associate professor of medicine at the University of Wisconsin, in the ASCO statement. "Therefore, limiting alcohol intake is a means to prevent cancer. The good news is that just like people wear sunscreen to limit their risk of skin cancer, limiting alcohol intake is one more thing people can do to reduce their overall risk of developing cancer." ◆

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FDA Action on MSK Tumor Profiling Assay Breaks Ground on Multiple Fronts

Mary Caffrey

THE FDA HAS AUTHORIZED a faster approval path for a next-generation sequencing (NGS) assay developed at Memorial Sloan Kettering (MSK) Cancer Center, which represents both a scientific and regulatory breakthrough at the agency.

The diagnostic test, known as IMPACT, identifies more genetic mutations, or biomarkers, for cancer "than any test previously reviewed by the agency," according to an FDA statement issued November 15.[1] What's more, the FDA simultaneously announced that it was granting accreditation to the New York State Department of Health (NYSDOH) to act on its behalf, and that tests that passed muster with that agency would not need a separate FDA clearance.

IMPACT, which stands for Integrated Mutation Profiling of Actionable Cancer Targets, allows clinicians to look beyond the mutations in solid tumor cancers—lung, colon, breast, and melanoma—to aid patients with less common solid tumors.[2] Because NGS casts a wider net than conventional genetic testing, it allows researchers in phase I "basket studies" to find out quickly if cancer therapies can be used in rarer cancers beyond those for which they are already approved.


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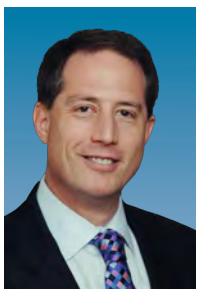
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The test had been submitted through the FDA's de novo premarket review pathway, reserved for low- to moderate-risk devices. It had previously been reviewed by NY state health regulators, who had cleared it for use. The FDA's action on November 15 created a Class II pathway for these types of tests, allowing them to be cleared either through the FDA or by an accredited third party.

Third-party accreditation allows the FDA to keep up with the pace of innovation and encourage test developers to voluntary seek 510(k) clearance, FDA Commissioner Scott Gottlieb, MD, said in the statement.

"This is another example of where the FDA is working to find creative and flexible approaches to regulation that spurs development and efficient delivery of innovative technology," he said. "We'll continue to look for opportunities to create regulatory efficiencies where possible to drive broader access to tools that improve American health, while maintaining the safety and efficacy standards that patients should expect from their FDA-reviewed products."[1]

"NGS technologies can examine hundreds, if not millions, of DNA variants at a time; and we are only at the beginning of realizing the true potential for these devices to assist patients and their health care providers in learning about the genetic underpinnings of their disease," said Jeffrey Shuren, MD, director of the FDA's Center for Devices and Radiological Health, in the statement.

"Recognizing the significant effect information about an individual's biomarkers can have on their care planning and outcomes, the FDA worked closely with NYSDOH and MSK to help ensure that the IMPACT test is accurate, reliable and clinically meaningful. This collaboration is an excellent example of how the FDA can partner with the medical and development communities to review innovative tests as quickly as possible." ◆

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ASCO's TAPUR Study Expands to Enroll Patients Receiving Immunotherapy

AJMC® Staff

WITH AN EXPANSION THAT includes immunotherapy combination treatments, the American Society of Clinical Oncology (ASCO)'s Targeted Agent and Profiling Utilization Registry (TAPUR) Study has now grown to 500 participants and 16 therapies.

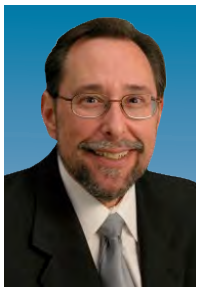
"This study just reached a key milestone and we're excited to explore these treatments further," said ASCO chief medical officer Richard L. Schilsky, MD, FACP, FASCO. "While no conclusions about drug efficacy should be drawn at this point, we are very pleased with the growth and expansion of the TAPUR Study."

The expansion now adds patients to the following study arms to TAPUR:

- Patients with ovarian cancer with *KRAS, NRAS,* and *BRAF* wildtype variants treated with cetuximab
- Patients with breast cancer with a high tumor mutation burden treated with pembrolizumab
- Patients with colorectal cancer with a *BRAF* V600E mutation treated with vemurafenib plus cobimetinib
- Patients with non–small cell lung cancer with CDKN2A deletion or mutation treated with palbociclib as monotherapy

The following study cohort, however, will be permanently closed:

- Patients with pancreatic cancer with CDKN2A loss or mutation treated with palbociclib as monotherapy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TAPUR, which provides patients access to drugs at no cost, is designed to evaluate FDA-approved targeted agents for indications other than those on the drug's label, with the objective of using real-world evidence to identify alternative options for patients with advanced disease.

According to the ASCO press release, 510 participants are enrolled in the TAPUR Study, which is available at 83 clinical sites in 20 states. The study now includes a new drug combination, nivolumab plus ipilimumab, an immunotherapy treatment that boosts the immune system to target tumor cells. With this addition, there are a total of 19 drugs yielding 16 different targeted therapy options (some drugs are used in combination).

"The TAPUR trial gives us the chance to [apply] the technology and the science, and apply it to patients in real time, with everybody agreeing that they're going to have access to the medicine, that they're going to have payment for the treatments, and that the data are going to be available," according to Leonard Lichtenfeld, MD, deputy chief medical officer, American Cancer Society. ◆

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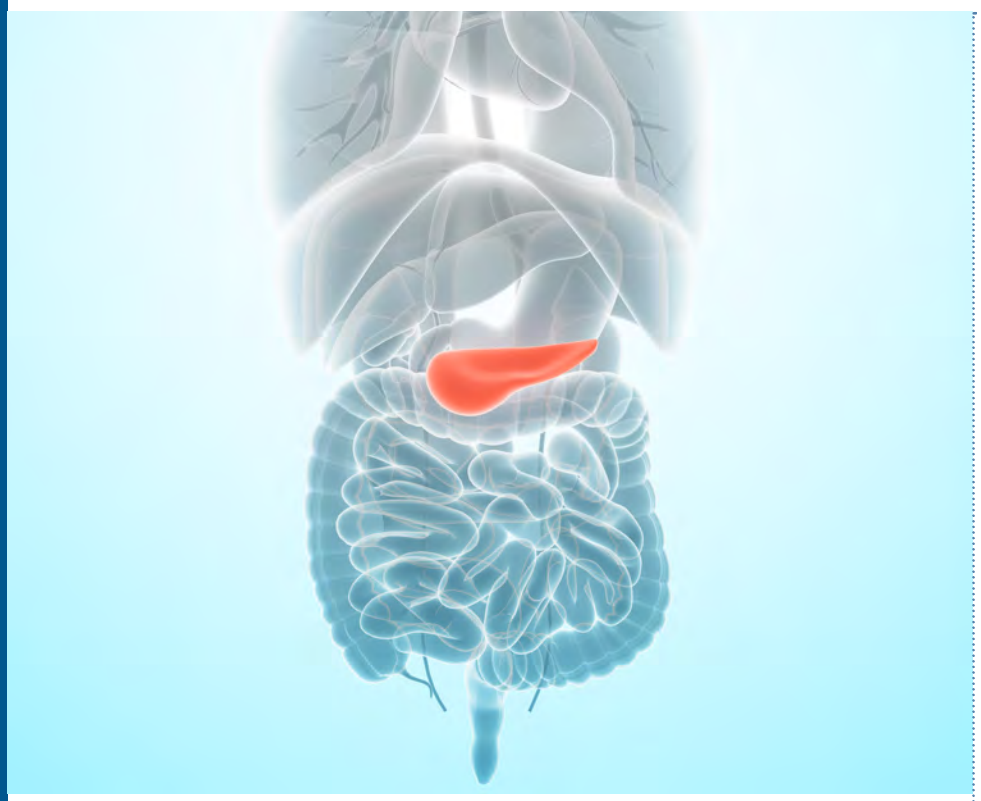
Study to Explore Link Between Diabetes, Pancreatic Cancer

Mary Caffrey

A 3-YEAR STUDY will investigate the link between new-onset diabetes and pancreatic cancer, with the hope of finding ways to detect pancreatic cancer early, when it is at a curable stage.

Richard Frank, MD, director of clinical cancer research for the Western Connecticut Health Network (WCHN), will lead the $2.7 million study, which will ask participants to undergo annual magnetic resonance imaging of »



the pancreas for 3 years under a protocol developed by network radiologists Ronald Lee, MD, and James Bauman, MD. A gastroenterologist will examine suspicious lesions using endoscopic ultrasound to determine whether cancer is present.

Study participants will also give a blood sample every 6 months to create a serum blood bank, which may later allow investigators to find a biomarker for pancreatic cancer; none currently exists.

Overtaking other types of cancer in overall death rate, pancreatic cancer is projected to be the second-leading cause of cancer death by 2020. A challenge with pancreatic cancer is that it is often detected only at a late stage, when it is difficult to treat.

Rising rates of diabetes and obesity have been linked to increases in pancreatic cancer. Type 2 diabetes is associated with a 1.5- to 2.0-fold increase in pancreatic cancer risk. Although the connection is not fully understood, insulin resistance, inflammation, and resulting hyperglycemia have been implicated in the mechanisms that cause cell proliferation in diabetes-related pancreatic cancer.

Insulin resistance, inflammation, and resulting hyperglycemia have been implicated in the mechanisms that cause cell proliferation in diabetes-related pancreatic cancer.

In 2012, Donghui Li, PhD, reported in *Molecular Carcinogenesis*[1] that results from animal studies suggest islet cell turnover, associated with insulin resistance, triggers the initial growth of pancreatic cancer cells. Because the failure of islet beta cells is the hallmark of the onset of obesity-associated type 2 diabetes, it would make sense to closely follow patients with new-onset diabetes for early signs of pancreatic cancer.

Patients in the trial will not have to pay for any tests, as all have been covered by private donations, according to a statement from WCHN. The actor James Naughton and his family raised more than $1 million for pancreatic cancer research in honor of his late wife, Pamela, who died of pancreatic cancer in 2013. ◆

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Fiber Intake Associated With Lower Mortality in Patients With Colorectal Cancer

Jaime Rosenberg

HIGHER FIBER INTAKE after the diagnosis of nonmetastatic colorectal cancer (CRC) is associated with lower CRC-specific and overall mortality, according to a study published in *JAMA Oncology*.

CRC is the third most common cancer and third-leading cause of cancer death in the United States. While high dietary fiber intake has previously been associated with a lower risk of CRC, there is no known benefit of fiber intake for CRC survivors.

"Due to lack of data on post-diagnostic diet and CRC survival, most dietary recommendations for CRC survivors are primarily based on incidence studies," wrote the authors. "Therefore, identifying prognostic dietary factors is needed to improve CRC survivorship."

Authors of the study analyzed 1575 healthcare professionals with stages I to III CRC from the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS). Participants were mailed a questionnaire focusing on medical history and lifestyle factors at baseline and every 2 years after.

Dietary data were collected and updated every 4 years using Food Frequency Questionnaires (FFQs). The baseline for NHS was 1980, and the baseline for HPFS was 1986. The study was conducted between December 23, 2016, and August 23, 2017.

Dietary fiber intake data collected by the FFQs inquired about how often, on average, the participant consumed each food of a specific serving size in the prior year. Authors calculated the daily intake for each nutrient by multiplying the reported frequency of consumption by its nutrient content and then summing across all foods.

CRC-specific and overall mortality was determined after adjusting for other potential predictors for cancer survival.

Results showed that high fiber intake was associated with lower mortality. The multivariable hazard ratio per 5-g increase in intake per day was 0.78 for CRC-specific mortality and 0.86 for all-cause mortality. The benefit of increasing fiber intake capped at approximately 24 g/d. Patients who increased their fiber intake after diagnosis had a lower mortality rate, with each 5-g/d increase in intake linked to an 18% lower CRC-specific mortality and 14% lower all-cause mortality.

There was no substantial association between fiber intake and tumor subsite or stage.

With respect to specific sources of fiber:

- Cereal fiber was associated with lower CRC-specific mortality and all-cause mortality.
- Vegetable fiber was associated with lower all-cause mortality but not CRC-specific mortality.
- Whole grain intake was associated with lower CRC-specific mortality.
- No association was found for fruit fiber.

"Our present study adds to the existing literature and suggests that the effect of high fiber intake may extend beyond protection against cancer incidence and contribute to better prognosis after cancer is established," concluded the authors. ◆

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Do Oral Parity Laws Reduce OOP Spending for Patients?

Surabhi Dangi-Garimella, PhD

ACCORDING TO A NEW ANALYSIS by Stacie Dusetzina, PhD, and colleagues, state oral parity laws—devised to equate out-of-pocket (OOP) spending for patients, irrespective of whether their treatment is an oral agent or an infusion—are not consistent with reducing patient OOP costs for oral anticancer agents.

The medical versus pharmacy benefit equation has shifted for these oral agents. John Fox, MD, MHA, senior medical director and vice president of medical affairs, Priority Health, explained during a panel discussion hosted by *The American Journal of Managed Care*® that more than 60% of patients on the commercial side of their plans have significant deductibles and coinsurance. "There is less cost sharing on the pharmacy benefit for an oral cancer drug than on the medical benefit, but an unintended consequence of this is that oral prices may increase for patients."[1]


FOX

For the present study, published in *JAMA Oncology*,[2] investigators at the University of North Carolina, Harvard Medical School, and Brigham and Women's Hospital analyzed claims data from 3 insurance plans for the period between 2008 and 2012, aggregated by the Health Care Cost Institute. The nearly 64,000 adults in the study lived in 1 of 16 states that passed the oral parity laws during the study period and had received anticancer treatment for which an oral option was available. Primary outcomes being evaluated were:

- Anticancer medication use
- OOP spending
- Total healthcare spending

The use of oral anticancer agents, measured as a percentage of overall anticancer treatment, rose from 18% to 22% during the study period, in the months prior to and after parity. Prescription fills for oral therapies without a co-pay rose from 15.0% to 53.0% among plans subject to parity, compared with a 12.3% to 18.0% increase in plans not subject to parity (P<.001).

Additionally, patients with monthly OOP spends of over $100 increased from 8.4% to 11.1% in plans subject to parity, while those not subject to parity saw a slight decline: 12.0% to 11.7% (P = .004). Importantly, patient monthly OOP spending varied based on the actual OOP amount after parity:

- Spending decreased by $19.44 at the 25th percentile.
- Spending decreased by $32.13 at the 50th percentile.
- Spending decreased by $10.83 at the 75th percentile.
- Spending increased by $37.19 at the 90th percentile.
- Spending increased by $143.25 at the 95th percentile.
- The 6-month total spending did not change post parity for oral or any anticancer therapy users.

Based on their results, the authors concluded that, despite the slight financial protection, "parity laws may not be sufficient to ensure that patients are protected from high out-of-pocket medication costs." ◆

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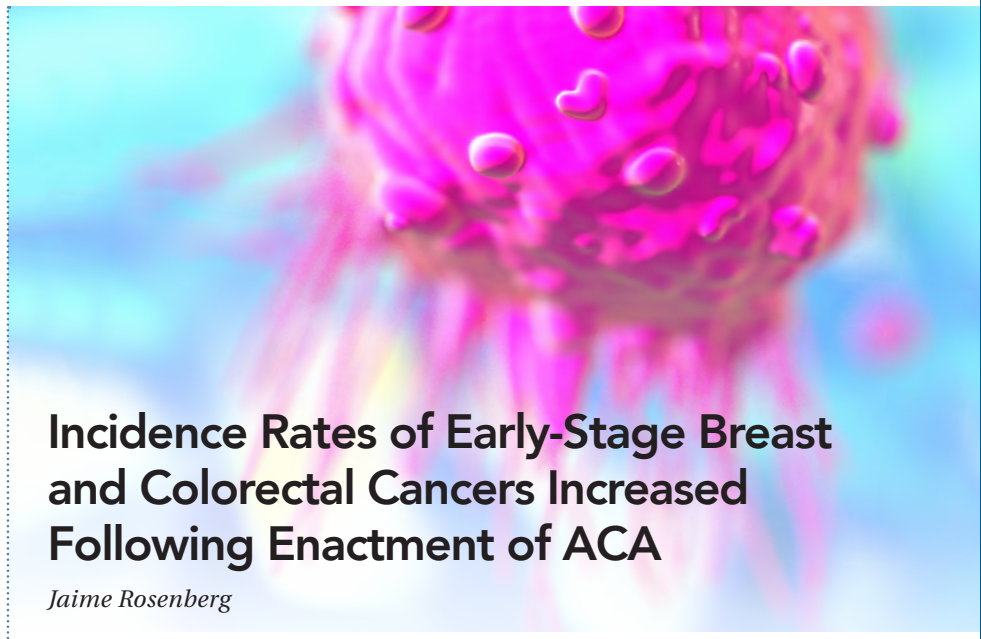

Incidence Rates of Early-Stage Breast and Colorectal Cancers Increased Following Enactment of ACA

Jaime Rosenberg

THE INCIDENCE RATES of early-stage breast and colorectal cancers increased after the initiation of the Affordable Care Act (ACA), according to a study published in *JAMA Oncology*.

In addition to expanding insurance coverage, the ACA puts emphasis on preventive care. Through the ACA, cost sharing for services given an A or a B grade by the US Preventive Services Task Force (USPTF) is eliminated.

"Although these policies have improved preventive care generally, their impact on cancer screening specifically is uncertain," wrote the authors.

The authors of the study analyzed incidence rates in early-stage breast, colorectal, and cervical cancers following the implementation of major ACA policies on January 1, 2014.

The 3 types of cancers all have A or B screening grades from the USPSTF.

Age-adjusted incidence rates of the 3 types of cancers were compared in the first 9 months of 2013 (pre-ACA) and the last 9 months of 2014 (post-ACA), with an intervening 6-month "wash-in" period.

Incidence rates were per 100,000 person-years and were age adjusted. The authors computed the incidence rate ratios (IRRs) and associated 95% confidence intervals to assess for change between the pre- and post-ACA periods. Weighted least squares with a log link were used to see whether the relative difference in IRRs for early-stage disease varied significantly compared with locally advanced/metastatic disease. To find the relative difference in IRRs, the authors exponentiated the difference-in-differences of the log IRRs.

The authors found that from pre- to post-ACA, the incidence of early-stage breast cancer increased from 55.5 to 56.9 cases per 100,000 person-years, with an IRR of 1.025. The incidence of early-stage colorectal cancer (CRC) increased from 13.5 to 15.3 cases per 100,000 person-years, with a pre- to post-ACA IRR of 1.132.

The difference in IRRs was significantly greater for early versus locally advanced/metastatic stages in both early-stage breast cancer and CRC. However, this pattern was not seen in cervical cancer.

These results showed that following the adoption of the ACA, the incidence of early-stage breast and CRC increased but did not vary for the late stages of the 2 cancer types. Although the screening itself was not assessed, these findings are consistent with increased breast and CRC screenings since the ACA was enacted.

"These results are consistent with a small but positive impact of the ACA on use of recommended cancer screening, which may vary by cancer site," concluded the authors. ◆

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Produced by Laura Joszt and The Center for Biosimilars®

Tesh Khullar: Community Oncologists Need to Understand Impact of Biosimilars on Their Business

Tesh Khullar serves as Flatiron Health's senior vice president for provider solutions. He said that biosimilars for core therapeutics are being approved and community oncologists must understand how that affects their business and reimbursement.

What potential changes should community oncologists keep an eye on that might affect their business?

Biosimilars are coming out. In fact, the first biosimilar in a core therapeutic just got approved, and it's Avastin [bevacizumab]. Before this, we've only seen biosimilars in supportive care. It's easier for an oncologist to make the jump of, "Hey, it's not core chemo, I'm going to be using a biosimilar as a supportive care, and using a, let's say, Zarxio instead of a Neupogen." But now that they've got to make that same jump from a core chemotherapy drug like Avastin, which is a monoclonal antibody, it's a lot more difficult to recreate. But with the argument on the biosimilar front, it's going to be interesting to see how this all pans out. What is Amgen going to do around contracting with the oncology practices, trying to create differential against the incumbent, which is Genentech? It will be really interesting to see what happens.

There's a public policy decision—the comment period, unfortunately, already ended—but they're trying to link the J code associated with all the biosimilars. So, biosimilar Teva will have the same J code as biosimilar Dr. Reddy, which will have the same as the biosimilar that Amgen makes. The issue with that is it's going to lead to the ASP [average sales price] dropping faster, and from an economic standpoint, you won't have the financial benefit anymore. Maybe that's OK in a value-based care world. I just don't think we're there yet. And the government should understand, as long as fee-for-service still exists and the core reimbursement mechanism of ASP still exists, they shouldn't just delink and learn from biosimilars. They should treat it like the generic it's probably closer to, like the European Union does, and then let community oncology unfold and understand the economics from that perspective.

I know the American Medical Association already wrote a letter against this; pharma has commented on it as well. Legislation like that, around key things that affect the business, need to be understood by community oncology. ◆

Amanda Forys on the Need for Clarity in Biosimilars

Amanda Forys, MSPH, discussed the critical lack of clarity in the US biosimilars marketplace and policy issues that are being overlooked.

Is there a specific policy that's missing from the biosimilars market?

I think there are several areas that manufacturers are looking for clarification in and bringing biosimilars to market around the patent dance and a lot of other different things that the FDA still has to put out guidance on. But one of the biggest payment policy issues that I think is being ignored right now, that will be an issue as more products come to market, is how biosimilar products are being treated under Medicare Part D. Currently, if you are taking a branded product and you hit the doughnut hole, and you've spent—now you're responsible technically to pay the full cost of your drug—well, the coverage gap is closing now and manufacturers can offer this discount for you to help you get out of the doughnut hole but not have to pay the full cost of your drug.

So, if a drug was $100 before, the patient would have paid $100 and that money would have counted toward their true out-of-pocket and gotten them through to the catastrophic [coverage limit]. Once they get into catastrophic coverage, they are only responsible for 5% of their drug cost. Well, with the coverage gap discount program, the manufacturer said, we will now pay 50% of the drug cost, the patient will pay 45% of the drug cost, and then the plan kicks in the final 5%. That's how the coverage gap will close by 2020. That money though, that the manufacturer is giving to the patient, counts as their true out-of-pocket cost. Biosimilars are not considered branded products in the eyes of Medicare for non–low-income subsidy beneficiaries. So, when they hit that coverage gap, the drug will be treated as a generic product instead of as a branded product. Now the patient will have to pay a higher percentage relative to what they would have paid if the product was treated as a branded product and what the plan is picking up. Now it's a share between what the plan and the patient have to pay. What the plan is picking up does not count toward that troop and helping the patient get into the doughnut hole, because we are seeing a lot of these products coming out right now that are on the Part B side and not on the Part D side.

There really hasn't been a final answer on was that the intent of this or have we just not addressed it yet? I think manufacturers will be looking for that guidance moving forward. For low-income subsidy [LIS] patients, a biosimilar is counted as a branded product, so they do pay a higher co-pay when they access the drug if someone is an LIS beneficiary. This inconsistency is definitely something that will need to be addressed in the future. Not just LIS, but for the Medicare program as a whole. ◆

Dr Ira Klein Outlines the Biggest Challenge of Value-Based Drug Pricing

Ira Klein, MD, MBA, FACP, senior vice president of healthcare quality strategy for the Strategic Customer Care Group at Janssen Pharmaceuticals, reported that the healthcare industry is becoming more proficient at value-based pricing arrangements. Even if they never dominate the market, Klein said there is a place for them.

What are some challenges of value-based drug pricing?

I think the biggest challenge is that of acquiring the appropriate information to make sure that if you're in a value-based agreement, you're hitting your quality marks, your outcomes measures, [and] your cost measures. The sheer difficulty in aggregating data over time in a select population has made it tough to get value-based agreements to become the norm. Because if you think about the amount of money either saved or lost, if the administrative burden is larger than the gains or losses, then respective parties will decide not to have those agreements in place.

However, I believe that we are learning how to do these agreements in ways that are more administratively efficient, to focus on areas of mutual agreement, where both parties can actually have elements of outcomes and performance that are desired for their end goals and thus will have some additional value-based agreements in the marketplace.

It may never dominate the marketplace, but it will always be a factor because it's a signal and a harbinger for other things that need to change in our healthcare delivery world and in the entire supply chain—from manufacturer to [group purchasing organization] to provider to patient. ◆

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Terrill Jordan: Education and Data Are Key for OCM Success

Education is the key to success in the Oncology Care Model (OCM), but presenting data in a simple format for clinicians to use is also critical, said Terrill Jordan, CEO, of Regional Cancer Care Associates.

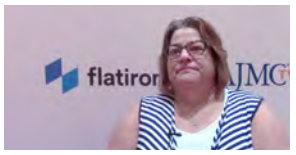
What are some best practices for implementing the OCM?

Our best practices have been the education of our clinicians. You must consistently educate, educate, educate. We also learned that the data were important, being able to get data and then make it simple on very simple dashboards. We have clinicians who work anywhere from 12- to 15-hour days, their staff is stretched thin, they don't have a lot of time to go through lots of data. So, you have to simplify it so they can spend their time focused on just what they need so they can get back to their patients.

We do find that data is what they're looking for. They find it enlightening and sometimes surprising. And it's always exciting to see how they respond to it. ◆

Teri Kovach on What to Do During an EHR Disruption

A practice must be ready for any disruption to its electronic health record (EHR) and have a plan in place, even if this does not occur often, said Teri Kovach, RN, OCN, compliance officer and charge nurse at Salish Cancer Center, in Fife, Washington.



What is the disruption in a practice if the EHR isn't working or there is a glitch in the system?

The disruption if your EHR is not working is that you're going to go to paper and pencil, and that's going to slow everything down because pharmacy has all their boxes that they need to tick off before they will take a drug and put it into circulation. And the computer systems speak to each other, so when one is not speaking, nobody is speaking, and then it just kind of shuts everything down and everyone runs around like they're chasing their tail because they can't figure out "What do we do now? How do we do this?"

It's old school. You just go back to, "Here are the forms." We have a hold down time policy that I wrote before we ever went live so that we would be ready in the event that that's happened, and we have not had to use it. It's there if we need it, but we haven't had to use it yet.

What's the best way to ensure a smooth implementation of a new EHR?

Keep the staff involved the entire time. We had certain people that were involved in the process, and they were the key people from departments and a lot of the peripheral staff, which should have been involved from day 1 [but] were not involved. So, as they're learning, they're seeing it for the first time and it didn't flow very well. You really have to have every single person that's going to be touching that EHR to be involved and be working in the practice field. If that means you have to sit down and look over their shoulder and watch them go through the process to see that they can do it, [that] would be perfect. ◆

Dr Amy Abernethy on Improving Patient Access to Oncology Clinical Trials

As oncology moves toward deeper diagnostic testing and as standard of care continues to quickly evolve, technology advancements are necessary to continue to improve patient access to clinical trials, explained Amy Abernethy, MD, PhD, the chief medical officer, chief scientific officer, and senior vice president of oncology at Flatiron Health.

How does oncology benefit from improving patient access to clinical trials?

How does oncology benefit more from the technology innovations of now and in the future than perhaps other therapeutic areas?

I think it's several things. First, what we are seeing in oncology is more and more deep diagnostic testing, such as next-generation sequencing testing. The more that we have details of the patient and specific requirements for each protocol, such as a specific biomarker and finding that out in the patient's biomarker testing and those 2 things can be linked up—that's going to be specific to disease areas like oncology and rare disease. So, I think that's one place where trials have been particularly tough. It's sort of this rare patient finding, the needle-in-the-haystack problem, that is pretty unique to oncology.

Another place that is particularly hard within oncology is that the standard of care is rapidly changing, and so clinical trials that have control arms that reflect standard of care from yesteryear, that's not going to work for us in oncology. I can't afford to take care of my patient and my patient can't afford for me to take care of him or her using old fashioned treatments. Being able to design clinical trials in oncology that either use data and data-informed standard of care so that it's as contemporary as possible and perhaps doesn't even need to expose this particular patient to that kind of standard of care, but rather just the novel treatments, are the kinds of things they need in oncology. ◆

Documenting When a Patient Falls Outside a Recommended Pathway

Documenting when a patient falls outside of a recommended pathway has the dual benefits of improving the algorithm and helping a provider get reimbursed faster, explained Torrie K. Shields, MPH, senior program manager of Palliative Care Program Design & Implementation for Blue Shield of California.

How does digital data help when a patient falls outside of a recommended pathway?

When a patient falls outside of that pathway, the first thing is making sure it's documented why you made a difference choice. That can feed back into the algorithm that helps people better understand what types of patients respond to what types of treatment, and it could essentially create a new pathway, and a more nuanced focus on personalized medicine. So, we're able to feed data back in when we are able to document somebody falling outside that.

It helps a provider in terms of audit, or in explaining to a payer, a financier, about why they went outside of that pathway, and that creates a dialogue that really focuses on change or quality improvement, rather than on incentives and mandates. When a payer, especially when we're moving to value-based payment, knows why somebody went outside of a pathway, they're able to look at it differently and assess and respond and pay/reimburse faster. ◆

PHYSICIAN-PATIENT INTERACTION

EHR Documentation and the Patient–Physician Visit

Sheree Starrett, MD, MS

continued from cover

The following are key highlights from the IOM report:

- The ability to access patient data without delay at any time in any place (eg, in an emergency or when the patient is away from home)
- Ensure that services are obtained and track outcomes of treatment
- Aggregate data from large numbers of patients, both to measure outcomes of treatment and to promptly recognize complications of new drugs, devices, and treatments

To achieve these results, systems would need to be "patient specific, allow population-based analyses, and have systems that manage the case process through reminder, decision support, and guidance grounded in evidence-based knowledge."[1]

In 2001, the IOM published *Crossing the Quality Chasm: A New Health System for the 21st Century*, which furthered the concept that using information technology would greatly improve healthcare quality.[2] The report stressed "the importance of a strong information infrastructure in supporting efforts to reengineer care processes; manage the burgeoning clinical knowledge base; coordinate patient care across clinicians, settings, and over time; support multidisciplinary team functioning; and facilitate performance and outcome measurements for improvement and accountability."[2]

Despite the IOM's belief that greater use of information technology and computerized records would improve healthcare quality, adoption of electronic record keeping remained slow. In 2001, only 18% of medical practices in the United States were using some form of an electronic health record (EHR). The HITECH Act of 2009 greatly spurred EHR implementation by offering financial incentives for adoption and penalties for failure to comply. Consequently, 78% of community practices in the United States had started using some form of EHRs by 2013,[3] with the prediction that 90% of practices would have EHRs by 2017.[4]

Unintended Consequences

Unfortunately, the significant increase in the amount of data to be collected has created 2 unplanned consequences. For many practices, physicians became responsible for collecting this explosion of required data during the patient visit. This has caused them to spend more time doing data entry and clerical tasks than clinical activities. One study showed that "for every hour a physician spent providing direct clinical care to patients, he or she spent nearly 2 hours on EHR and other desk work, plus another 1 to 2 hours each night."[5] Another study reported the actual effect on physician well-being when the time allotted for a visit did not meet the actual time required to accomplish all the required tasks. These time pressures increased the following: "stress, satisfaction, burnout and intent to leave practice."[6] The problem of increased risk of physician burnout with EHR usage was confirmed in a 2016 report.[7]

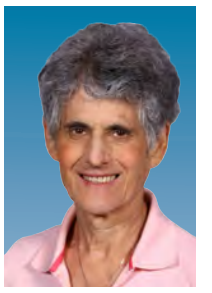
The other unintended consequence for patient care was how the physical task of using computers or other electronic devices during a patient visit could adversely affect the quality of patient–physician communication. In 2005, Ventres et al related that physicians using EHRs were more occupied with data gathering and clarifying clinical information than listening to patients' own narratives. They were more prone to neglecting patients' agendas" and less likely to "explore psychosocial and emotional issues or discuss how health problems affect patients' lives." Using the computer also created other problems, with physicians spending more time staring at the monitor or intensely keyboarding, rather than interacting with the patient.[8]

Nowhere in medicine is effective patient–physician communication more vital than in the relationship between oncologists and their patients. A cancer diagnosis creates great stress and uncertainty. Patients need to be able to understand complex information about their illness and its possible treatments, and they are often required to make life-altering decisions. Patients depend on their oncologists to help them in all these areas.[9]

Unintended consequences of increased EHR use include less focus on the patient, more physician time on data collection, and burnout.

With electronic record keeping, patients are finding themselves sharing the physician's time and attention with the computer, turning what used to be a "dyadic" relationship between patient and physician to a triadic relationship of patient, physician, and computer.[10] Investigators write that patients across the globe have a "major concern about computers in the office—the fixation of the physician's eyes on the computer screen." This fear was not unfounded, as a study by Margalit et al found that physicians spent an average of 24% to 55% of the time gazing at the screen during a patient's visit.[11]

Research has confirmed that the use of the computer during the office visit takes away from the goal of patient-centered care. Even the simple task of introductions and starting a visit was affected by the presence of the computer: investigators found that after a short greeting, physicians walked straight to the computer, rather than interacting with the patient or discussing the patient's agenda.[12] »



STARRETT

Sheree Starrett, MD, MS, is a board-certified hematologist/oncologist and a former medical director with Aetna.

What the physicians saw on the computer screen often prompted their opening statement, failing to ask the patient to share his or her concern(s).[12]

Street et al noted that using the computer during the visit led physicians to focus more on information-related tasks and less on psychosocial issues.[13] They also found that physicians busy filling out check boxes in the EHR reduced the number of open-ended questions they asked patients and that multitasking caused physicians to lose focus and compromise effective communication.[13]

Interventions to Improve Patient–Physician Computer Interactions

While physicians can control, to a variable extent, their choice of hardware and software and their communication style, they have little to no control over the amount of data collection mandated by external stakeholders (payers, governmental organizations, external review organizations, vendors and suppliers, etc). Recognizing the burden of administrative tasks on physicians, the American College of Physicians' Medical Practice and Quality Committee issued a white paper on the need for all external stakeholders to review the value and necessity for all the information being collected and whether some of the data can be eliminated or decreased. The paper emphasized that this needs to be an ongoing process, not simply a onetime effort.[14]

Unfortunately, physician choice of hardware and software is very much influenced by cost. Purchase of software updates and training on how to use the software are added practice expenses, over and above unforeseen expenses such as changes in computer equipment and exam room layout.

Physicians need to appreciate the effect that EHR charting and documenting has had on physician–patient communication—they need to understand that paying excessive attention to the computer and EHR may cause them to lose focus on their patients. Physicians must recognize that certain behaviors under their control are not acceptable. "Looking predominantly at the computer monitor during office visits, typing while patients are talking about intimate concerns, reading silently from the monitor while patients sit idly, using templates to lead interviewing rather than listening to patient narratives, and having their backs to patients" all work against relationship building.[15]

In their 2013 paper, How to Integrate the Electronic Health Record and Patient-Centered Communication Into the Medical Visit: A Skills-Based Approach, Duke et al presented 10 behaviors or interventions physicians should follow when using an EHR.[10]

- Changing the location of the EHR's computer screen is a fairly easy intervention. Ideally, exam room screens should be located in a position that allows physicians to maintain patient eye contact and avoid having their backs to patients.
- Similarly, the ability to share the screen and its information with the patient is another positive for effective communication.[16]
- A crucial skill that is under physicians' control is their ability to type and their familiarity with their own EHR. As less computer-savvy physicians retire, the problems of poor typing and slowness with mouse clicks will disappear. In the meantime, all physicians using EHRs should make every effort to become proficient at typing and using computer hardware and know the capabilities and functionalities of their own EHR program.
- Ideally, physicians should have reviewed their patient's records before starting any encounter. Upon starting a visit, they should introduce themselves and their role in the patient's care. It is also useful for the physician to introduce the patient to the electronic record and explain that he or she might be typing into the computer during the course of the visit.
- A major pitfall to avoid is allowing the EHR template to dictate the course of the visit. Physicians need to start with open-ended questions and collaborate with the patient on what is to be accomplished during the course of the visit. Statements such as "Excuse me a second while I type this into the record," "Just give me a minute while I look at the computer—I want to make sure I get this down correctly," and "Let me tell you what I am typing" are ways to involve patients in what one is doing when focused on the computer and not the patients.[10] Physicians should explain to the patients when questions specific to templates or required data elements must be entered into the EHR.
- Physicians need to be able to follow patient cues and emotions and know when to interrupt typing and devote their complete attention to their patients. Research has shown that "emotional aspects of the interview are best accomplished when the physician moves her head, eyes, and torso toward the patient; removes her hands from the keyboard or mouse; pushes the monitor away; and gives the patient her undivided attention."[10]

One of the major advantages of the computer for clinical practice and for oncology specialists is the ability to educate patients about their condition and to share information. The physician can point to the screen and offer to visually share test results, lab findings with trends, or x-ray tests. Additionally, information on treatments and possible clinical trials can be found and printed out for the patient. This ability to readily share the information in the EHR is a major benefit and facilitator of patient engagement.

Conclusion

The transition from paper-based office records to documentation using electronic media has had several unplanned consequences. Physicians are finding themselves spending more time on data entry and looking at computer screens than on focusing on patients. While the EHR has greatly improved the ability to share information and educate patients, it has also had a negative impact on patient centeredness and emotional and psychological communication and the ability to establish a trusting relationship between physicians and patients. This article outlines practical ways to use the computer in a positive way. ◆

AUTHOR INFORMATION

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

*Based on market share data from IMS from November 2016 to April 2017.
†Based on market share data from IMS from May 2014 to April 2017.

CLL
SLL

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in 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.

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

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

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

Hypertension: Hypertension (range, 6 to 17%) has occurred in patients treated with IMBRUVICA® with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®.

Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

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

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

Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation

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 10/17 PRC-03138

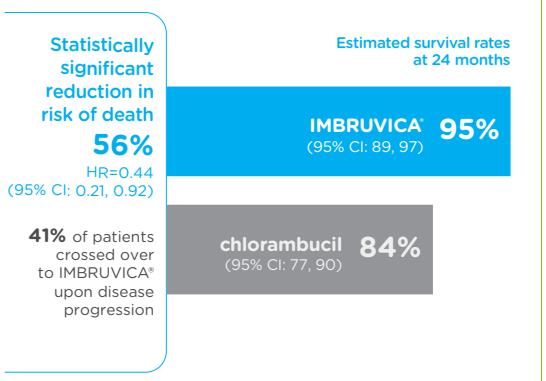
RESONATE™-2 FRONTLINE DATA

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

EXTENDED OVERALL SURVIVAL[2]

SECONDARY ENDPOINT: OS
IMBRUVICA® vs CHLORAMBUCIL

Reduced risk of death by more than half

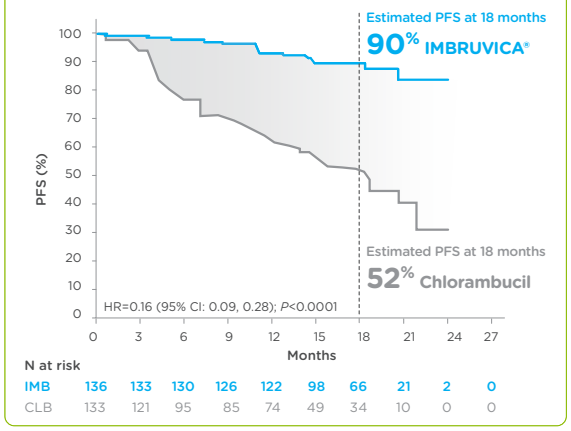


- Median follow-up was 28 months[2]
- Fewer deaths with IMBRUVICA® were observed; 11 (8.1%) in the IMBRUVICA® arm vs 21 (15.8%) in the chlorambucil arm[2]

PROLONGED PROGRESSION-FREE SURVIVAL[2,3]

PRIMARY ENDPOINT: PFS
IMBRUVICA® vs CHLORAMBUCIL

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



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

RESONATE™-2 Adverse Reactions ≥15%

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

of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

B-cell malignancies: The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (62%), neutropenia (61%), diarrhea (43%), anemia (41%), musculoskeletal pain (30%), rash (30%), bruising (30%), nausea (29%), fatigue (29%), hemorrhage (22%), and pyrexia (21%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (39%), thrombocytopenia (16%), and pneumonia (10%).

Approximately 6% (CLL/SLL), 14% (MCL), 11% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4%-10% (CLL/SLL), 9% (MCL), and 9 % (WM [6%] and MZL [13%]) of patients discontinued due to adverse reactions.

cGVHD: The most common adverse reactions (≥20%) in patients with cGVHD were fatigue (57%), bruising (40%), diarrhea (36%), thrombocytopenia (33%), muscle spasms (29%), stomatitis (29%), nausea (26%), hemorrhage (26%), anemia (24%), and pneumonia (21%).

The most common Grade 3 or 4 adverse reactions (≥5%) reported in patients with cGVHD were fatigue (12%), diarrhea (10%), neutropenia (10%), pneumonia (10%), sepsis (10%), hypokalemia (7%), headache (5%), musculoskeletal pain (5%), and pyrexia (5%).

Twenty-four percent of patients receiving IMBRUVICA® in the cGVHD trial discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 26% of patients.

DRUG INTERACTIONS

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

CYP3A Inhibitors: Dose adjustment may be recommended.

SPECIFIC POPULATIONS

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

Please see the Brief Summary on the following pages.

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

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

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INDICATIONS AND USAGE

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

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

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) *[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 adult 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 adult patients with Waldenström's macroglobulinemia (WM) *[see Clinical Studies (14.3) in Full Prescribing Information]*.

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

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

Chronic Graft versus Host Disease: IMBRUVICA is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy *[see Clinical Studies (14.5) 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 (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 29% of patients *[see Adverse Reactions]*. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

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

Monitor complete blood counts monthly.

Atrial Fibrillation: Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

Hypertension: Hypertension (range, 6 to 17%) has occurred in patients treated with IMBRUVICA with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

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

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

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations]*.

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

* Based on laboratory measurements and adverse reactions

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

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

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

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

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

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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies*	12*	0
Vascular disorders	Hypertension	16	8

* One patient death due to histiocytic sarcoma.

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

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

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

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

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

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

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

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

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

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

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

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

IMBRUVICA® (ibrutinib) capsules

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

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular Disorders				
Hypertension*	14	4	1	0
Nervous System Disorders				
Headache	12	1	10	2

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

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

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

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

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

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

Waldenström's Macroglobulinemia and Marginal Zone Lymphoma: The data described below reflect exposure to IMBRUVICA in open-label clinical trials that included 63 patients with previously treated WM (Study 1118) and 63 patients with previously treated MZL (Study 1121).

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

Nine percent of patients receiving IMBRUVICA across Studies 1118 and 1121 discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 10% of patients.

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

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 (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

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 (N=63) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection Sinusitis Pneumonia* Skin infection*	19 19 14 14	0 0 6 2
Respiratory, thoracic and mediastinal disorders	Epistaxis Cough	19 13	0 0
Nervous system disorders	Dizziness Headache	14 13	0 0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

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

Table 10: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with WM in Study 1118 (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

Study 1121: Adverse reactions and laboratory abnormalities described below in Tables 11 and 12 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

Table 11: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 1121 (N=63)

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

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

Table 12: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with MZL in Study 1121 (N=63)

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

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

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

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

Adverse reactions and laboratory abnormalities described below in Tables 13 and 14 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 13: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions	Fatigue Pyrexia Edema peripheral	57 17 12	12 5 0
Skin and subcutaneous tissue disorders	Bruising* Rash*	40 12	0 0
Gastrointestinal disorders	Diarrhea Stomatitis* Nausea Constipation	36 29 26 12	10 2 0 0
Musculoskeletal and connective tissue disorders	Muscle spasms Musculoskeletal pain*	29 14	2 5
Vascular disorders	Hemorrhage*	26	0
Infections and infestations	Pneumonia* Upper respiratory tract infection Sepsis*	21 19 10	10 0 10

Table 13: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4(%)
Nervous system disorders	Headache	17	5
Injury, poisoning and procedural complications	Fall	17	0
Respiratory, thoracic and mediastinal disorders	Cough Dyspnea	14 12	0 2
Metabolism and nutrition disorders	Hypokalemia	12	7

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

Table 14: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

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

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

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

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

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

DRUG INTERACTIONS

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

Examples[a] of strong CYP3A inhibitors include: boceprevir, clarithromycin, cobicistat conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, and troleandomycin.

Examples[a] of moderate CYP3A inhibitors include: aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, and verapamil.

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

Patients with B-cell Malignancies: *Posaconazole:* Reduce IMBRUVICA dose to 140 mg once daily during coadministration with posaconazole at doses of no more than 200 mg BID *[see Dosage and Administration (2.4) in Full Prescribing Information]*. Avoid the coadministration of IMBRUVICA with posaconazole at doses of greater than 200 mg BID.

Voriconazole: Reduce IMBRUVICA dose to 140 mg once daily during coadministration with any dose of voriconazole *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Other Strong Inhibitors: Avoid concomitant administration of IMBRUVICA with other strong CYP3A inhibitors. Alternatively, interrupt IMBRUVICA therapy during the duration of strong CYP3A inhibitors if the inhibitor will be used short-term (such as anti-infectives for seven days or less) *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Moderate Inhibitors: Reduce IMBRUVICA dose to 140 mg once daily during coadministration with any moderate CYP3A inhibitor *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Monitor patients taking concomitant strong or moderate CYP3A inhibitors more frequently for adverse reactions of IMBRUVICA.

Patients with Chronic Graft versus Host Disease: *Moderate CYP3A Inhibitor:* Modify the dose based on adverse reactions *[see Dosage and Administration (2.3) in Full Prescribing Information]* for patients coadministered IMBRUVICA with any moderate CYP3A inhibitor.

Strong CYP3A Inhibitors: Reduce IMBRUVICA dose to 280 mg once daily for patients coadministered IMBRUVICA with

- posaconazole immediate-release tablet 200 mg BID or
- posaconazole delayed-release tablet 300 mg QD or
- voriconazole any dose

Modify the dose based on adverse reactions *[see Dosage and Administration (2.3) in Full Prescribing Information]*

Avoid concomitant administration of IMBRUVICA with posaconazole at higher doses and other strong CYP3A inhibitors. If these CYP3A inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA therapy during the duration of the inhibitor *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Effect of CYP3A Inducers on Ibrutinib: The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Examples[a] of strong CYP3A inducers include: carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and St. John's wort[b].

[a] These examples are a guide and not considered a comprehensive list of all possible drugs that may fit this category. The healthcare provider should consult appropriate references for comprehensive information.

[b] The induction potency of St. John's wort may vary widely based on preparation.

USE IN SPECIFIC POPULATIONS

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

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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

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

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

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

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

Contraception

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

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

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

Geriatric Use: Of the 905 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 21% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades) and Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA.

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

Monitor patients for adverse reactions of IMBRUVICA and follow dose modification guidance as needed. *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information].*

Plasmapheresis: Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA.

Modifications to IMBRUVICA dosing are not required.

PATIENT COUNSELING INFORMATION

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

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

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PRC-03045

TRIAL ENROLLMENT

How Technology, Social Media Are Changing the Way Clinical Trials Connect With Patients

Mary Caffrey

TAN

EHRENBERG

SHPILBERG

Belinda Tan, MD, PhD, top, is the co-founder and chief medical officer of Science 37.

Evan Ehrenberg, PhD, middle, is the co-founder and CEO of Clara Health.

Sandra Shpilberg, MBA, below, is the founder and CEO of Seeker Health.

continued from cover

the rules of engagement that connect researchers with patients for clinical trials. In the process, company leaders say they are not only shaving months off recruitment schedules, but also finding more patients from minority groups and from rural areas. Studies show these populations need more representation in trials.[3-5]

Technology is poised to do more than change the way patients are recruited for clinical trials, however. As Belinda Tan, MD, PhD, co-founder and chief medical officer of Science 37, explained to *EBO*™, integrating telehealth and personal health technologies, like smartphones or Apple Watches, will further erode barriers to participation. Patients can be supervised remotely, with assistance from a local physician or nurse, while study drugs are shipped directly to their homes. Besides patient recruitment, Science 37's NORA platform (nor connection to Nora Therapeutics) for Network Oriented Research Assistant, meets FDA digital signature requirements[6] and helps pharmaceutical sponsors with digital data collection.[6] Tan's fellow co-founder, Noah Craft, MD, PhD, DTMH, has said the minority enrollment in Science 37's cancer trial pools is 3 times that of a standard trial.[7]

Tan saw what NORA could do in 2015, when Genentech used the platform to create 1 "meta-site" among more than 60 in a large international clinical trial. Science 37 was contracted to recruit 5 patients a year but instead recruited twice that number. "That was a huge win," Tan said. "It was just a case scenario of what we could do."

Even if they are not yet using telehealth for virtual trials, pharmaceutical companies can use digital tools like Apple's ResearchKit to develop their own apps to connect with patients and collect data on patient-reported outcomes.[8]

Right now, there isn't much collaboration with payers in this area, but those on the leading edge say there's no reason why this can't change. In particular, Tan would like to see solutions for hurdles in trials that require patients to already have had gene sequencing, which payers won't fund.

Democratizing Clinical Trials

Both Shpilberg and Clara Health co-founder and CEO Evan Ehrenberg, PhD, say that unlike recruitment methods of old, these new strategies start with the patient. "For a long time, we've had a physician-centered approach—almost all the referrals came from hospital sites," Ehrenberg told *EBO*™ in an interview. Putting patients in "the driver's seat," is crucial, he said, because sometimes physicians don't know about every trial or don't have an incentive to refer their patient to one based outside the academic center where they practice.

Contrast this with a process that starts with patients seeing what Shpilberg calls a "patient-friendly" ad on Facebook, which connects that person directly to a set of prescreening questions to find out if he or she is a potential fit. "We're turning the process upside down," she said.

Clara Health shares an enormous amount of content with users. Its website[9] has information on every trial registered on ClinicalTrials.gov, and it seeks to match patients with trials not only by condition, but also with help from an online digital assistant who offers to chat with users when they reach the site. Clara Health also features blogs about the clinical trial process to educate patients or caregivers.

When the company works with pharmaceutical sponsors, "our role is to make the trial as easy to access as possible," Ehrenberg said. The presentation on ClinicalTrials.gov doesn't tell patients what to do if they find an appropriate trial. In the past, if a patient found a phone number for a study coordinator on the site, it might only be answered during business hours.

"If patients have a serious medical condition, they just give up," he said. Clara Health's role is to take the "heavy lifting" out of the enrollment process to keep patients engaged. When necessary, the company can connect patients with groups that pay for travel and expenses to take part in a trial, and it also helps patients apply for financial assistance.

Language matters, Ehrenberg said, and it's something Clara Health is trying to change. "We encourage our sponsors, when they talk about participants, to treat them like people, as opposed to just numbers," he said. "A lot of times that doesn't happen; perhaps their IRB [Institutional Review Board] thinks it isn't appropriate… but we don't think people should be referred to as 'test subjects.'"

Modern Marketing, Meeting IRB Standards

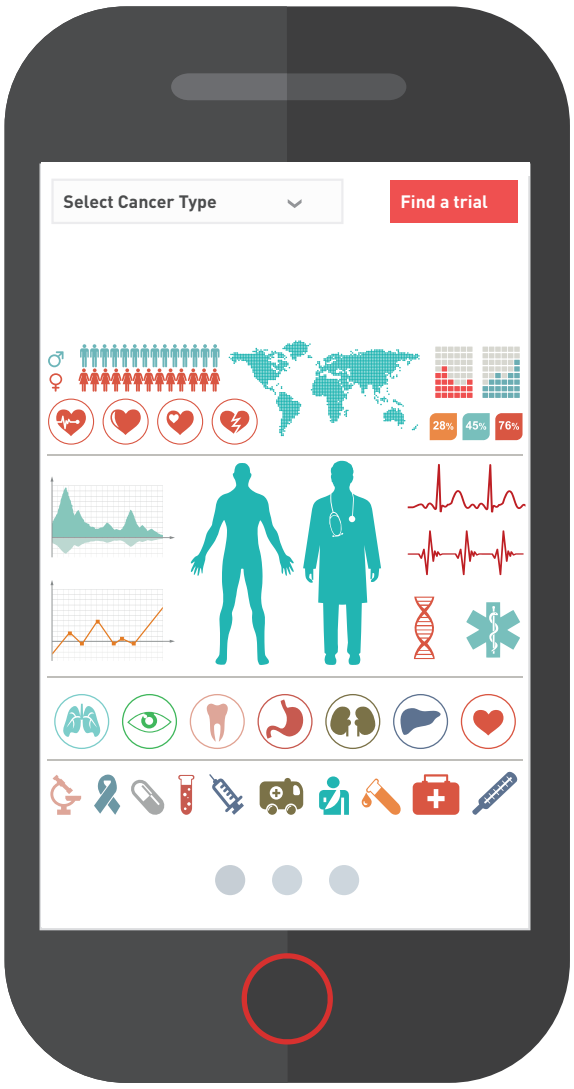
Two years in, Seeker Health has been involved in 22 clinical trials, with about 40% in oncology therapies, 40% in rare disease, and 20% in women's health therapies, Shpilberg said. In the process, it has developed standards for reaching out to patients in cost-effective ways that still pass muster with IRBs. Seeker Health can target ads at subpopulations that have previously shown an interest in specific cancers or rare diseases, and it can even target them by finding common threads among these groups of potential patients that have nothing to do with their medical condition. For example, in the first venture, Shpilberg discovered the group of women she was seeking favored a popular novel, and that offered another recruitment path.

At the same time, Seeker Health must take steps to keep prospective trial participants from being swayed by factors other than the ad itself. Seeker Health employs a tool that achieves "comment suppression," which means that even if an online user tries to comment on the ad, those statements remain hidden from other users. This way, Shpilberg said, no misinformation about the study or the drug is spread online.

Are new regulations needed? Shpilberg says no; all ads must meet existing FDA requirements for enrolling patients, as well as privacy regulations under the Health Insurance Portability and Accountability Act and the Health Information Technology for Economic and Clinical Health Act. A June 2017 document published by Harvard Catalyst, based on a paper published in the *American Journal of Bioethics*, spells out the relevant issues for IRBs and researchers and concludes that no new regulations are needed.[10,11]

Reducing Costs, Targeting Discrete Cancer Types

Both Shpilberg and Science 37's Tan said cutting months out of the enrollment process will translate into savings and allow pharmaceutical companies to bring products to market faster. If technology



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Virtual trial assistants, such as those provided by Clara Health, can be a tremendous resource for patients and caregivers. This can also provide a significant boost to the clinical trial recruitment process.

offers solutions to rising recruitment costs, this could reverse a trend that has frustrated all parts of the research chain.

A 2016 study prepared for HHS said that maintaining research sites accounted for 9% to 14% of clinical trial costs.[12] Another report from Pivotal Financial Consulting LLC found that the percentage of recruited patients who ended up enrolling in trials was declining, and that "unproductive" costs accounted for 66% of what pharmaceutical companies spend on trials.[13]

Thus, Tan said, the shift toward virtual trials could do something more—it could help smaller biotechs compete by letting them know quickly whether further studies are worth pursuing.

"The benefit of being fast is that it gives enough evidence, enough of a signal to go out and get more investors, or it gives companies confidence to shift resources to something they know has more promise," Tan said. "If there's no signal of efficacy there, they can say, 'OK, let's not waste more time on this.'"

Oncology, especially, she said, begs for this type of model, where small companies can work on discrete solutions but find patients from all over—and conduct virtual trials with patients supervised in tandem with a local physician. "In cancer, people have talked about how the decentralized trial model would be ideal. We're going to have more targeted therapies, more molecular [DNA] signatures," she said.

"Ultimately," Tan said, "as cancer becomes more like a rare disease, where the percentage of people with a particular pathway with a molecular mutation is very small, you can use this model to reach an entire base of people and not be limited by geography, by having to go to the local cancer center. This becomes a more tenable type of trial to do." ◆

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PATIENT-REPORTED OUTCOMES

Q&A With Dr Thomas LeBlanc: The Value of ePROs in Oncology

Surabhi Dangi-Garimella, PhD

LEBLANC

Thomas W. LeBlanc, MD, is medical oncologist, Duke University School of Medicine.

continued from cover

***EBO™*: Could you provide a brief introduction to PROs, their influence on the cancer drug development process, and the subsequent influence on cancer care overall?**

LEBLANC: PROs are validated tools that help provide additional information about what patients are going through and how they are feeling. Until relatively recently, these were mostly just tools used in research studies. Patient-reported outcome measures of things like health-related quality of life include different domains about how a person is functioning physically, about what symptoms they're going through, their emotional state, their social well-being, and so on.

The FDA, too, has recognized that this aspect of measuring the patient experience was missing from the drug development process. They have increasingly been saying that PROs need to be part of what we measure when we test new drugs or compare drugs, and it's an important part of what should be in the repertoire of clinical trial end points. While traditional clinical trial end points—remission rate, complete response to chemotherapy, overall survival [OS], and event-free survival—are all very important, other kinds of end points, such as what happens to someone's overall health-related quality of life when they get treatment A versus the standard treatment, are important as well. If all things are equal, if people live about the same length of time, what is that time like? Is the time potentially better? Is it worse because of side effects?

PROs are an important way to amplify the patient voice as part of what's going on in clinical trials.

***EBO™*: Are PROs usually secondary or tertiary end points in a clinical trial? What is their influence on the outcome of a trial?**

LEBLANC: There are several recent examples of PRO measures being important in the drug approval process, and [they are among] the things we review in our paper.[1] There is a drug called ruxolitinib, indicated for the rare blood cancer myelofibrosis, that was approved in large part because it dramatically improved a PRO measure called the total symptom score scale [TSS]. Patients with myelofibrosis have really debilitating symptoms: They have spleen enlargement that pushes on their stomach, so they feel full all the time; as a result they don't eat well, they lose a lot of weight, and they experience other constitutional symptoms such as fever and dramatic fatigue. A lot of these things were improved with this new medication. So, although ruxolitinib met some traditional end points too, such as improved OS, some of the earlier, more exciting, and interesting findings really had to with TSS, and that was a big part of the story around the drug getting approved.

Similarly, another story we mention in the paper is the approval of a chemotherapy for pancreatic cancer, gemcitabine, which was compared with the standard treatment at that time, 5-fluorouracil. While gemcitabine improved overall survival, it also improved a composite measure that evaluated patients' experiences, including pain, maintenance of physical function, and weight loss, among other things—our paper describes this in detail. These are just a couple of examples where in the last few decades the patient voice, through PROs, has become so much more important in how we count what is a meaningful difference with a new treatment.

***EBO™*: In your paper, you discuss how ePROs could make it easier for patients or their family caregivers to participate in the process of reporting the patient experience. Can you tell us more?**

LEBLANC: Electronic PROs are the next frontier in the field. The big distinction here is what happens on research studies and clinical trials versus what can just happen in how we take care of people. For me, what's most exciting about ePROs is that they can be a part of good cancer care, or medical care, and not simply a clinical trial tool.

A few recent examples have shown that using ePRO methods for people with advanced cancer enhances our ability to take care of them. One such landmark study, which we refer to in our paper, was done by Dr Ethan Basch and published in the *Journal of Clinical Oncology*,[2] regarding its quality-of-life end points, and then more recently in *JAMA*, regarding the survival measures from that study.[3]

What the authors did was electronic symptom monitoring on a weekly basis. So, when people were home, they were filling out a questionnaire about 12 common symptoms; the results were relayed back to the care team and to nurses who could then intervene and not have to wait for the person to call or show up in the emergency department [ED] to get help. It's almost like an early warning system for people with cancer, whereby reporting their experiences and symptom burden between visits led to improvements in overall quality of life, fewer ED visits, and then eventually about a 5-month survival benefit. In patients with advanced solid tumors, it's quite remarkable.

That's about what we expect to see with new therapies for advanced solid tumors—and this wasn't a treatment, it was just improved monitoring and better care. That's why I like to say that ePROs really amplify the patient voice and help us to better see the patient experience to incorporate it into what we are doing for that person to provide excellent cancer care to them.

***EBO™*: How do you ensure that the most important PROs are being collected but that the patient is not burdened?**

LEBLANC: The issue of survey overload is really the big one that we are facing now in this part of the field. We can measure anything and everything at this point—there is a PRO for so many different things—but you can't ask every patient 250 questions on a weekly basis, daily basis, or every time they come to the clinic, because people quickly get tired of it.

Part of what we wrote about in our paper,[1] though, is that the recipe to success with PROs seems to be not so much related to how many questions you ask people, but rather if you make it useful to them to answer those questions. What I mean by that is that we found when the answers to the questions impact the care that people receive, that is a reinforcing experience. So, if patients realize, "My doctor actually looked at this, and cares about the result, and cares about how I am feeling. This is a way for me to communicate things that we didn't have time to talk about in a short visit; my doctor went over these things with me that I said were really bothering me during the next visit, and I can see that

it actually changed the care that I received, it helped me be heard in ways that maybe I wouldn't have been," that's important.

In 1 of our analyses, we evaluated the completeness of questionnaire batteries and people getting PRO assessments as part of routine care, here at Duke, and found a significant correlation, such that people who weren't likely to come back for a consult were a lot less likely to fill out the questions. On the other hand, among people who filled out the questions and then realized that it changed the care they received, the completion rates were more than 90%. They always filled it out at subsequent visits because they realized it was an important part of coming to the clinic and us being able to take good care of people by knowing what's going on with them and how they are feeling.

***EBO™*: What are some of the challenges of collecting PROs in the clinic?**

LeBLANC: One of the major challenges is the work flow. Everyone is really busy in oncology clinics, and if you do something where you create a new app, and the patient has to download and use it, and then the doctor has to use it as they are also trying to do everything else they are supposed to do in a 10-minute visit, which is already too much, then it just won't work. They are struggling with documentation and the electronic health record [EHR]—if the app doesn't integrate with the electronic record, then nobody is going to use it. It doesn't matter how much money you spend developing an amazing app; if it doesn't really make things easier for the clinicians and the patients, then it will not be used, or will not be viewed as being helpful.

The other issue is the EHR itself. Despite the advancements, EHRs are quite problematic in fundamental ways. Each is a bit different, but I have yet to see one that really does a good job of providing an off-the-shelf PRO module, or that does it in a way that works well in real-world practice. For example, with the system that we are using here at Duke, I can send out electronic questionnaires to patients automatically before a visit. However, I can't necessarily control what the data look like when they come back to me—I can't control where they go in the chart, and they don't come back in ways that I find particularly useful for patient care. EHR vendors have not really stepped up to the plate on this issue, which has resulted in the development of homegrown PRO systems in the clinic, which creates other problems with sustainability. I hope to see this change in the coming years.

***EBO™*: Is there a challenge in bringing providers on board to be a part of this process?**

LeBLANC: It is very much a challenge. There is a lot of activation energy required to change what you do. Anyone who comes in and says, "Now we are going to start collecting this new questionnaire and we want you to use it in clinic," is perceived as someone who is just telling you to do more work when you are already overworked. That's a recipe for failure with busy clinicians.

Incorporating PROs in the clinic will require buy-in at every level—from not only the patients, but the clinicians who are there in the trenches. When I am in my clinic and I am running an hour late through no fault of my own—maybe the lab is running behind or I had a patient who was very sick and I needed to spend some extra time with them—the last thing that I am going to do then is spend extra time on something else that isn't required for me to take care of a person. If the change does not save time or is not well-integrated into people's workflows, then it will be perceived as difficult or not helpful, and people will rally against it. This is especially true if they don't recognize its value.

An ideal example of this is symptom screening. A part of what clinicians do when they see patients is a "review of systems" assessment, which includes queries on different types of symptoms and issues and about whether they are bothering a patient. Well, PRO systems can, and should, do that, but that would mean that the PROs would have to be collected in the waiting room or before a patient's clinic visit, and then be presented back to the clinician in a useful way that doesn't create confusion, slowdowns, or extra work.

> **"We know from other studies that patients are much more accurate about reporting their experience of illness than doctors or other clinicians are, who to some degree are guessing at what they think people are going through."**
>
> —Thomas W. LeBlanc, MD

However, if someone hands them an iPad and asks them to fill it out while they are in an exam room, then nobody can see them until they are done, and that holds up other patients from being put in the room and slows down clinicians—it's not going to fly. But if PROs are collected when the patient is sitting in the waiting room, and then integrated into the EHR in a way that also pulls it into their clinical documentation so the clinician has all of those data at their fingertips during the examination, and saves time when writing their notes, then you have streamlined care. It would improve efficiency as well as the quality of the information.

We know from other studies that patients are much more accurate about reporting their experience of illness than doctors or other clinicians are, who to some degree are guessing at what they think people are going through. It's important to recognize that. Patients are the experts on their own experiences.

***EBO™*: Do you think the physician on-boarding with respect to PROs can be spearheaded by payers?**

LeBLANC: That's a tough question. There has been some discussion about including PRO measures as part of value-based care in pay-for-performance initiatives. I've heard more about these things in surgical settings, such as postoperative clinics, looking at different PRO measures around functional status and quality of life as hallmarks of whether you provided good care. But this could go wrong, in some unfair ways. Imagine you see a patient who has a joint replacement and then they just don't do their rehabilitation program, and then end up with poor mobility and maybe pain; that doesn't mean that you provided bad care, it means the patient didn't do their part. That's an instance where you can see the folly of a PRO measure being related to reimbursement, or perceptions of value of care. Is it reasonable to do that kind of assessment and then hold physicians accountable? I'm concerned about that possibility and what that might look like. Similarly, we might expect PROs to worsen steadily over time in people with advanced cancer, and it doesn't mean we provided bad care but rather that the disease and its treatments take a toll over time. So, what might be the right PROs to track in a pay-for-performance kind of way? I'm not sure.

On the other hand, there may be instances, say in the cancer care setting, where we might think it's more agreeable to use more specific PRO measures around what a person is going through—for example, a measure of nausea or vomiting in people who are getting chemotherapy. There are standard protocols for preventing chemotherapy-induced nausea and vomiting, plus we now have really effective drugs. While we probably won't get to a zero rate where nobody has either of those side effects, sometimes we may not do as well as we could or should be doing to prevent them. If we actually measured the rate of these side effects and if practices were held accountable to that, I can guarantee you they would pay more attention to it, and get much better at addressing the issue than they are now. That is 1 example where a very focused measure could be quite helpful and very appropriate.

***EBO™*: What are your predictions for the growth of this field?**

LeBLANC: Overall, PRO measures are very useful tools for amplifying the patient's voice as part of their cancer care. That's a voice that often gets muted and stifled in how we take care of people. We know that our healthcare system is not set up to be patient-friendly—it's built around clinicians and nurses rather than patients, ultimately.

Inclusion of PROs into routine care will improve patient care by increasing emphasis on the patient experience—what they go through, how they feel, and how they live when they are not in the clinic. Most of these people's lives, when they are dealing with something like cancer, is spent mostly outside of the clinic; we only see them a few days a month. What's going on during these other times, that's where PROs can be very helpful in amplifying the patient voice and making us pay attention to the patient experience in ways we unfortunately tend not to in routine cancer care today. ◆

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