SPECIAL ISSUE: **PALLIATIVE CARE** FEATURING CONFERENCE COVERAGE: **ACCC**

AJMC® THE AMERICAN JOURNAL OF MANAGED CARE®

25 YEARS RESEARCH & LEADERSHIP

Evidence-Based ONCOLOGY™

APRIL 2020
VOL. 26 • NO. 4

ALSO IN THIS ISSUE

DYING WITHOUT FEAR. Kashyap Patel, MD, oncologist with Carolina Blood and Cancer Care Associates and associate editor of Evidence-Based Oncology™, has published an account of his efforts to engage patients on the topic that was never covered in medical school: facing death. A review, SP106.

CARE CONNECTIONS. A session of the Institute for Value-Based Medicine in Tampa, Florida, with Florida Cancer Specialists covered how payers, oncologists, and leaders in primary care can cooperate for the benefit of patients, SP109.

ACCC MEETS. One of the last conferences to take place before in-person medical meetings were canceled, the Association of Community Cancer Centers gathered March 4 to 6, 2020, in Washington, DC. For full coverage, see SP111-SP113.

OUR EXPERTS. *AJMC*® catches up with leading physicians and advocates to discuss palliative care and the transition to the Oncology Care First model, SP122-SP123.

DIGITAL TECHNOLOGY

The Need for a Serious Illness Digital Ecosystem (SIDE) to Improve Outcomes for Patients Receiving Palliative and Hospice Care

Jonathan Nicolla, MBA; Hayden B. Bosworth, PhD; Sharron L. Docherty, PhD, PNP-BC; Kathryn I. Pollak, PhD; Jeremy Powell, MEd; Nichole Sellers, BA; Bryce B. Reeve, PhD; Greg Samsa, PhD; Linda Sutton, MD; and Arif H. Kamal, MD, MBA, MHS

Introduction

Palliative and hospice care services produce well-known benefits for patients living with serious illness and for their families. Benefits include improved quality of life and reduced symptom burden, spiritual and emotional distress, and caregiver distress.[1] Additionally, when integrated into usual care, palliative and hospice services result in savings to patients, caregivers, payers, and health systems, particularly from reducing avoidable hospital admissions and emergency department visits.[1]

Pillars of Model

CONTINUED ON SP124 »

FRONTIERS IN CARE

Why Palliative Care Is the Answer to the Serious Illness Question in Payment Reform

Maggie R. Salinger MD, MPP; Nathan A. Boucher, DrPH, PA, MS, MPA; Thomas W. LeBlanc, MD, MA; Kevin C. Oeffinger, MD; Kathryn Pollak, PhD; Jesse D. Troy, PhD; and Arif H. Kamal MD, MBA, MHS

FOLLOWING ENACTMENT OF the Patient Protection and Affordable Care Act, the Center for Medicare & Medicaid Innovation (CMMI) was established to design and analyze payment models that would replace a fee-for-service reimbursement structure. To that end, CMMI launched reimbursement programs that use risk-adjusted budgets alongside quality-driven rewards to promote value and innovation at the care delivery level. These came to be known as alternative payment models (APMs).

CONTINUED ON SP127 »

REIMBURSEMENT

Lack of Clarity on Medicare Advantage Palliative, Other Cancer Care Benefits Limits Consumer Uptake

Ted Knutson and Mary Caffrey

STARTING IN 2019, Medicare Advantage (MA) plans were allowed to change with the times and offer new social benefits to support patients with serious illness or chronic conditions, such as home-based palliative care.[1]

But the lack of clarity about these benefits has limited uptake by consumers, experts say. In December, CMS proposed funding the hospice benefit differently, which would allow MA plans to "carve in" to this benefit. Although some say this could help seniors in the long run, in the near term it has created uncertainty about how the government will fund care for the seriously ill.[2]

CONTINUED ON SP130 »

AJMC® Managed Markets Network®
ACCC Association of Community Cancer Centers
AJMC® THE INSTITUTE FOR VALUE-BASED MEDICINE®
COA COMMUNITY ONCOLOGY ALLIANCE

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients exposed to IMBRUVICA® in 27 clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 39% of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. In IMBRUVICA® clinical trials, 3.1% of patients taking IMBRUVICA® without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding.

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

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 24% of 1,124 patients exposed to IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

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

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

Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA® therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,124 patients exposed to IMBRUVICA® in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

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

Hypertension: Hypertension of any grade occurred in 12% of 1,124 patients treated with IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 5% of patients with a median time to onset of 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.

Second Primary Malignancies: Other malignancies (10%) including non-skin carcinomas (4%) have occurred in 1,124 patients treated with IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

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

Monitor patients closely and treat as appropriate.

pharmacyclics®
An AbbVie Company

janssen
PHARMACEUTICAL COMPANIES OF
Johnson & Johnson

LEADING THE WAY WITH A WAVE OF EVIDENCE

IMBRUVICA® is the only BTKi with 10 approvals, across 6 indications, based on 10 pivotal trials[1]

INDICATIONS

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

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

WM
- Waldenström's macroglobulinemia (WM)

cGVHD
- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy

MCL
- Mantle cell lymphoma (MCL) who have received at least one prior therapy*

MZL
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy*

*Accelerated approval was granted for the MCL and MZL indications based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial.

BTKi=Bruton's tyrosine kinase inhibitor.

Confidence built on 150,000+ patients treated worldwide[2†]

†Across all indications as of September 2019.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

B-cell malignancies: The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (58%)‡, diarrhea (41%), anemia (38%)‡, neutropenia (35%)‡, musculoskeletal pain (32%), rash (32%), bruising (31%), nausea (26%), fatigue (26%), hemorrhage (24%), and pyrexia (20%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (18%)‡, thrombocytopenia (16%)‡, and pneumonia (14%).

Approximately 7% (CLL/SLL), 14% (MCL), 14% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4-10% (CLL/SLL), 9% (MCL), and 7% (WM [5%] 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 higher adverse reactions (≥5%) reported in patients with cGVHD were pneumonia (14%), fatigue (12%), diarrhea (10%), neutropenia (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.

‡Treatment-emergent decreases (all grades) were based on laboratory measurements.

DRUG INTERACTIONS

CYP3A Inhibitors: Co-administration of IMBRUVICA® with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations. Dose modifications of IMBRUVICA® may be recommended when used concomitantly with posaconazole, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA® if strong inhibitors are used short-term (e.g., for ≤ 7 days). See dose modification guidelines in USPI sections 2.4 and 7.1.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

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

Please see brief summary on the following pages.

References: 1. IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC. 2019.
2. Data on file, REF-13821. Pharmacyclics LLC.

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

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

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

INDICATIONS AND USAGE

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

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

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

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

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

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

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

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients exposed to IMBRUVICA in 27 clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 39% of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA increases the risk of major hemorrhage. In IMBRUVICA clinical trials, 3.1% of patients taking IMBRUVICA without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding.

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

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 24% of 1,124 patients exposed to IMBRUVICA in clinical trials *[see Adverse Reactions].* Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

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

Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,124 patients exposed to IMBRUVICA in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. See Additional Important Adverse Reactions.

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

Hypertension: Hypertension of any grade occurred in 12% of 1,124 patients treated with IMBRUVICA in clinical trials. Grade 3 or greater hypertension occurred in 5% of patients with a median time to onset of 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA as appropriate.

Second Primary Malignancies: Other malignancies (10%) including non-skin carcinomas (4%) have occurred in 1,124 patients treated with IMBRUVICA in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
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	8†
	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	5†
	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

† Includes one event with a fatal outcome.

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

Treatment-emergent Grade 4 thrombocytopenia (6%) and neutropenia (13%) occurred in patients.

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 four randomized controlled clinical trials (RESONATE, RESONATE-2, and HELIOS, and iLLUMINATE) in patients with CLL/SLL (n=1,506 total and n=781 patients exposed to IMBRUVICA). Patients with creatinine clearance (CrCl) ≤ 30 mL/min, AST or ALT ≥ 2.5 x ULN (upper limit of normal), or total bilirubin ≥ 1.5x ULN (unless of non-hepatic origin) were excluded from these trials. Study 1102 included 51 patients with previously treated CLL/SLL, RESONATE included 386 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, RESONATE-2 included 267 randomized patients with treatment naïve-CLL or SLL who were 65 years or older and received single agent IMBRUVICA or chlorambucil, HELIOS included 574 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, and iLLUMINATE included 228 randomized patients with treatment naïve CLL who were 65 years or older or with coexisting medical conditions and received IMBRUVICA in combination with obinutuzumab or chlorambucil in combination with obinutuzumab.

The most commonly occurring adverse reactions in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, rash, musculoskeletal pain, bruising, nausea, fatigue, pyrexia, hemorrhage, and cough.

Four to 10 percent of patients with CLL/SLL receiving IMBRUVICA discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia. Adverse reactions leading to dose reduction occurred in approximately 7% 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 Higher (%)
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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
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	10	2†
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.
Treatment-emergent Grade 4 thrombocytopenia (8%) and neutropenia (12%) occurred in patients.

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 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 Higher (%)	All Grades (%)	Grade 3 or Higher (%)
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	2†
Infections and infestations				
Upper respiratory tract infection	16	1	11	2†
Pneumonia*	15	12†	13	10†
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
Muscle spasms	13	0	8	0
Respiratory, thoracic and mediastinal disorders				
Cough	19	0	23	1
Dyspnea	12	2	10	1
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

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
† Includes 3 events of pneumonia with fatal outcome in each arm, and 1 event of pyrexia and upper respiratory tract infection with a fatal outcome in the ofatumumab arm.

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

Treatment-emergent Grade 4 thrombocytopenia (2% in the IMBRUVICA arm vs 3% in the ofatumumab arm) and neutropenia (8% in the IMBRUVICA arm vs 8% in the ofatumumab arm) occurred in patients.

RESONATE-2: Adverse reactions and laboratory abnormalities described below in Tables 7 and 8 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in RESONATE-2.

IMBRUVICA® (ibrutinib)

Table 7: Adverse Reactions Reported in ≥ 10% of Patients 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 Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Nausea	22	1	39	1
Constipation	16	1	16	0
Stomatitis*	14	1	4	1
Vomiting	13	0	20	1
Abdominal pain	13	3	11	1
Dyspepsia	11	0	2	0
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				
Upper respiratory tract infection	17	2	17	2
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
Dyspnea	10	1	10	0
General disorders and administration site conditions				
Fatigue	30	1	38	5
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
Dizziness	11	0	12	1
Investigations				
Weight decreased	10	0	12	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 8: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE-2

	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	55	28	67	31
Platelets Decreased	47	7	58	14
Hemoglobin Decreased	36	0	39	2

Treatment-emergent Grade 4 thrombocytopenia (1% in the IMBRUVICA arm vs 3% in the chlorambucil arm) and neutropenia (11% in the IMBRUVICA arm vs 12% in the chlorambucil arm) occurred in patients.

HELIOS: Adverse reactions described below in Table 9 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 9: 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 Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	56†
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

Table 9: 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 (continued)

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
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%
† Includes 2 events of hemorrhage with fatal outcome in the IMBRUVICA arm and 1 event of neutropenia with a fatal outcome in the placebo + BR arm.

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.

iLLUMINATE: Adverse reactions described below in Table 10 reflect exposure to IMBRUVICA + obinutuzumab with a median duration of 29.3 months and exposure to chlorambucil + obinutuzumab with a median of 5.1 months in iLLUMINATE in patients with previously untreated CLL/SLL.

Table 10: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE

Body System Adverse Reaction	IMBRUVICA + Obinutuzumab (N=113)		Chlorambucil + Obinutuzumab (N=115)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Blood and lymphatic system disorders				
Neutropenia*	48	39	64	48
Thrombocytopenia*	36	19	28	11
Anemia	17	4	25	8
Skin and subcutaneous tissue disorders				
Rash*	36	3	11	0
Bruising*	32	3	3	0
Gastrointestinal Disorders				
Diarrhea	34	3	10	0
Constipation	16	0	12	1
Nausea	12	0	30	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain*	33	1	23	3
Arthralgia	22	1	10	0
Muscle spasms	13	0	6	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	27	1	12	0
Injury, Poisoning and Procedural Complications				
Infusion related reaction	25	2	58	8
Vascular disorders				
Hemorrhage*	25	1	9	0
Hypertension*	17	4	4	3
Infections and Infestations				
Pneumonia*	16	9	9	4†
Upper Respiratory Tract Infection	14	1	6	0
Skin infection*	13	1	3	0
Urinary tract infection	12	3	7	1
Nasopharyngitis	12	0	3	0
Conjunctivitis	11	0	2	0
Metabolism and Nutrition Disorders				
Hyperuricemia	13	1	0	0
Cardiac Disorders				
Atrial Fibrillation	12	5	0	0
General Disorders and Administration Site Conditions				
Pyrexia	19	2	26	1
Fatigue	18	0	17	2
Peripheral edema	12	0	7	0
Psychiatric disorders				
Insomnia	12	0	4	0

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
† Includes one event with a fatal outcome.

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

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

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

IMBRUVICA® (ibrutinib)

Study 1118 and INNOVATE Monotherapy Arm: Adverse reactions and laboratory abnormalities described below in Table 11 and Table 12 reflect exposure to IMBRUVICA with a median duration of 11.7 months in Study 1118 and 33 months in the INNOVATE Monotherapy Arm.

Table 11: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

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

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

Table 12: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

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

Treatment-emergent Grade 4 thrombocytopenia (4%) and neutropenia (7%) occurred in patients.

INNOVATE: Adverse reactions described below in Table 13 reflect exposure to IMBRUVICA + R with a median duration of 25.8 months and exposure to placebo + R with a median duration of 15.5 months in patients with treatment naïve or previously treated WM in INNOVATE.

Table 13: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with WM in INNOVATE

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

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.
† Includes one event with a fatal outcome.

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

Study 1121: Adverse reactions and laboratory abnormalities described below in Tables 14 and 15 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

Table 14: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 1121 (N=63)

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

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.
† Includes one event with a fatal outcome.

Table 15: 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

Treatment-emergent Grade 4 thrombocytopenia (3%) and neutropenia (6%) occurred in patients.

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 Table 16 and Table 17 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 16: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42)

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

The system organ class and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.
† Includes 2 events with a fatal outcome.

IMBRUVICA® (ibrutinib)

Table 17: 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

Treatment-emergent Grade 4 neutropenia occurred in 2% of patients.

Additional Important Adverse Reactions: *Cardiac Arrhythmias:* In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), the incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.5% and of Grade 3 or greater was 0.2% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of atrial fibrillation and atrial flutter of any grade was 9% versus 1.4% and for Grade 3 or greater was 4.1% versus 0.4% in patients treated with IMBRUVICA compared to patients in the control arm.

Diarrhea: In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), diarrhea of any grade occurred at a rate of 39% of patients treated with IMBRUVICA compared to 18% of patients in the control arm. Grade 3 diarrhea occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. The median time to first onset was 21 days (range, 0 to 708) versus 46 days (range, 0 to 492) for any grade diarrhea and 117 days (range, 3 to 414) versus 194 days (range, 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 85% versus 89% had complete resolution, and 15% versus 11% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 7 days (range, 1 to 655) versus 4 days (range, 1 to 367) for any grade diarrhea and 7 days (range, 1 to 78) versus 19 days (range, 1 to 56) for Grade 3 diarrhea in IMBRUVICA-treated subjects compared to the control arm, respectively. Less than 1% of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

Visual Disturbance: In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), blurred vision and decreased visual acuity of any grade occurred in 11% of patients treated with IMBRUVICA (10% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 6% in the control arm (6% Grade 1 and <1% Grade 2 and 3). The median time to first onset was 91 days (range, 0 to 617) versus 100 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 60% versus 71% had complete resolution and 40% versus 29% had not reported resolution at the time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution was 37 days (range, 1 to 457) versus 26 days (range, 1 to 721) in IMBRUVICA-treated subjects compared to the control arm, respectively.

Long-Term Safety: The safety data from long-term follow-up over 5 years of 1,178 patients (treatment-naïve CLL/SLL n=162, relapsed/refractory CLL/SLL n=646, and relapsed/refractory MCL n=370) treated with IMBRUVICA were analyzed. The median treatment duration for CLL/SLL was 51 months (range, 0.2 to 98 months). The median treatment duration for MCL was 11 months (range, 0 to 87 months). The cumulative rate of hypertension increased over time with prolonged IMBRUVICA treatment. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 6% (year 1-2), 8% (year 2-3), 9% (year 3-4), and 9% (year 4-5). The incidence for the 5-year period was 11%.

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

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

DRUG INTERACTIONS

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated

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

Lactation: *Risk Summary:* There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed child, 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:* Conduct pregnancy testing in 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 1,124 patients in clinical studies of IMBRUVICA, 64% were ≥ 65 years of age, while 23% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades), pneumonia (Grade 3 or higher), thrombocytopenia, hypertension, and atrial fibrillation occurred more frequently among older patients treated with IMBRUVICA.

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

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

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

PATIENT COUNSELING INFORMATION

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

- *Hemorrhage:* Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions].*
- *Infections:* Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Warnings and Precautions].*
- *Cardiac Arrhythmias:* Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions].*
- *Hypertension:* Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy *[see Warnings and Precautions].*
- *Second primary malignancies:* Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions].*
- *Tumor lysis syndrome:* Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions].*
- *Embryo-fetal toxicity:* Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA *[see Warnings and Precautions].*
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets approximately the same time each day *[see Dosage and Administration (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 doses to make up the missed dose *[see Dosage and Administration (2.6) in Full Prescribing Information].*
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions].* Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION .
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions].*
- Advise patients that they may experience loose stools or diarrhea and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration *[see Adverse Reactions].*

Active ingredient made in China.

Distributed and Marketed by:
Pharmacyclics LLC
Sunnyvale, CA USA 94085
and
Marketed by:
Janssen Biotech, Inc.
Horsham, PA USA 19044

Patent *http://www.imbruvica.com*

IMBRUVICA® is a registered trademark owned by Pharmacyclics LLC

PRC-06113

FROM THE EDITOR-IN-CHIEF

Putting the Patient Back at the Center of Patient-Centered Care

Tho' much is taken, much abides; and tho'
We are not now that strength which in old days
Moved earth and heaven, that which we are, we are;
One equal temper of heroic hearts,
Made weak by time and fate, but strong in will
To strive, to seek, to find, and not to yield.

Ulysses
Alfred Tennyson


ALVARNAS

AT THIS TIME OF breathtaking innovation in cancer diagnostics and therapeutics, it is easy to become distracted (even mesmerized) by the extraordinary advances in care technology to the point of losing sight of the fundamental fact that a patient's cancer journey is a human, not a technological, experience. Throughout the past 3 decades, as I have spoken with patients and their families about a new cancer diagnosis or a change in their goals of care, our discussions have never focused upon molecular biology, genomics, or abstract ideals about targeted drug design. I have yet to engage any patient or family in a discussion of the arcane details of any of the value-based care models. Instead, our discussions are focused on the more meaningful human dimensions of navigating the flood of emotion that stems from a cancer diagnosis; the focus is upon identifying grounded next steps; finding ways to chart a navigable, sustainable steps of a path that culminates in a restoration to wholeness. For some this is a journey that culminates in a cure; for others the focus is upon recovering a sense of wholeness for a patient and their family when a cure is no longer possible. Each patient travels their respective hero's journey. The reality is that our technological advancements are simply deployable tools for supporting the patient throughout that journey. How care we more effectively use these tools to humanize the cancer journey for patients and their families?

How can we put the patient back at the *center* of patient-centered care? How can we more effective and humanly support the patient's heroic journey? In this issue of *Evidence-Based Oncology*™ we explore the human dimensions of the cancer care experience in the hope of better understanding how better systems of care can more effectively serve patients and their families. Maggie L. Shaw provides us with the highlights from the Association of Community Cancer Centers' (ACCC) 46th Annual Meeting on disruptive, innovative ways to improve patient access to care. Jonathan Nicolla and colleagues discuss ways of using digital monitoring to more effectively assess outcomes for patients who are receiving palliative and hospice care. Maggie Salinger, MD, and her colleagues discuss the importance of payment reform in ensuring better and more effective access to palliative care. Finally, Florence Caffrey Bourg, PhD, reviews *Dying Without Fear: The Pursuit of Eternity* by Kashyap Patel, MD, which explores the deeply human nature of patients' cancer journeys.

Advances in care technology have indisputably improved patient outcomes, reduced treatment toxicities, and provided new opportunities for patients with advanced and relapsed cancers to live longer with a better quality of life. Our systems of care, however, have not evolved in ways that engender a more human care experience for either patients or their physicians. As clinicians navigate the near-infinite number of clicks needed to perform relatively simple care tasks on modern electronic health records and struggle to decipher the evolving rules of billing and reimbursement, the precious left to spend with our patients and their families is increasingly compromised by indifferent systems of care, many of which ironically claim to be patient-centered. In *Ulysses,* Tennyson writes of the transcendent strength that can arise when we first acknowledge the pain, fragility, and humanness that form the underpinnings of our journey. Building systems of care that acknowledge and build upon this are essential to realize the aspiration of delivering truly patient-centered care. ◆

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.

www.ajmc.com/about/ebo
EBOncology

SPECIAL ISSUE / Palliative Care
APRIL 2020
VOLUME 26, ISSUE 4

CONTINUED ON SP103 »

WHO ARE THE *AJMC*® STRATEGIC ALLIANCE PARTNERS?
This symbol designates authors and faculty from our Strategic Alliance Partners®, who work with us to share important news and insights in oncology, reimbursement, and other areas. If your organization would like to become a Strategic Alliance Partner, email MARYCAFFREY@AJMC.COM with SAP in the subject field.

AJMC®
THE AMERICAN JOURNAL OF MANAGED CARE®

PUBLICATION STAFF
ASSOCIATE EDITORIAL DIRECTOR
Mary K. Caffrey
SENIOR EDITOR
Allison Inserro
ASSOCIATE EDITOR
Maggie L. Shaw
PROJECT MANAGER
Andrea Szeszko
COPY CHIEF
Jennifer Potash
COPY SUPERVISOR
Paul Silverman
MEDICAL & SCIENTIFIC QUALITY REVIEW EDITOR
Stacey Abels, PhD
COPY EDITORS
Rachelle Laliberte
Kirstin Mackay
Amy Oravec
Holly Poulos
CREATIVE DIRECTOR, PUBLISHING
Ray Pelesko
SENIOR ART DIRECTOR
Melissa Feinen
ART DIRECTOR
Julianne Costello

SALES & MARKETING
VICE PRESIDENT
Gilbert Hernandez
NATIONAL ACCOUNT MANAGER
Ryan O'Leary
NATIONAL ACCOUNT ASSOCIATE
Kevin George

OPERATIONS & FINANCE
CIRCULATION DIRECTOR
Jon Severn
VICE PRESIDENT, FINANCE
Leah Babitz, CPA
CONTROLLER
Katherine Wyckoff

CORPORATE OFFICERS
CHAIRMAN & FOUNDER
Mike Hennessy Sr
VICE CHAIRMAN
Jack Lepping
PRESIDENT & CEO
Mike Hennessy Jr
CHIEF FINANCIAL OFFICER
Neil Glasser, CPA/CFE
EXECUTIVE VICE PRESIDENT, OPERATIONS
Tom Tolvé
SENIOR VICE PRESIDENT, CONTENT
Silas Inman
SENIOR VICE PRESIDENT, I.T. & ENTERPRISE SYSTEMS
John Moricone
SENIOR VICE PRESIDENT, AUDIENCE GENERATION & PRODUCT FULFILLMENT
VICE PRESIDENT,
Joy Puzzo
VICE PRESIDENT, HUMAN RESOURCES AND ADMINISTRATION
Shari Lundenberg
VICE PRESIDENT, BUSINESS INTELLIGENCE
Chris Hennessy
VICE PRESIDENT, MARKETING
Amy Erdman
EXECUTIVE CREATIVE DIRECTOR, CREATIVE SERVICES
Jeff Brown

Scan here to subscribe
ajmc.com/subscribe.

AN MJH life sciences™ BRAND

2 Clarke Drive, Suite 100
Cranbury, NJ 08512 • (609) 716-7777

The American Journal of Managed Care® ISSN 1088-0224 (print) & ISSN 1936-2692 (online) is published monthly by Managed Care & Healthcare Communications, LLC, 2 Clarke Drive, Suite 100, Cranbury, NJ 08512.

FROM THE CHAIRMAN

Making Palliative Care the Norm Starts With the Doctors

LAST SUMMER, *Evidence-Based Oncology*™ Associate Editor Kashyap Patel, MD, noted that it had been 5 years since our journal had devoted an issue to palliative care, and it was time to revisit this important "patient-centered" topic. Our issue would coincide with the release of his book, *Dying Without Fear*, which chronicles his effort to help a special patient take control of his own fate, despite limited options. Patel does not run from the hard conversations; rather, he has made it his mission late in his career to run toward them, to fill in the gaps so common in standard medical training.

Cancer patients want palliative care, even if they don't know what to call it. They want the supportive care, the spiritual guidance, the information about their options—the good news and the bad news. They might not want to be flooded with information the minute they are diagnosed, but when they have had time to think, they want help making decisions. Jeffrey Lowenkron, MD, MPP, Chief Medical Officer, The Villages Health, said so during an interview at the Institute for Value-Based Medicine in Tampa, Florida. And guess what? Lowenkron says primary care physicians do a lousy job of talking to patients about what they want.

The only group that's worse at helping patients with advanced care planning, he said, are oncologists. For cancer patients or survivors, "the likelihood that they'll get palliative care at the right time or even hospice at the right time, I would say it's unfortunately delayed."

It doesn't have to be this way. Reimbursement structures are shifting to value-based models that reward those who take their time and counsel patients appropriately. While not common enough, physician training is becoming available. And, as we read in the review of Patel's book, there are other well-established fields that offer rigorous, standards-driven models.

While better reimbursement models are important—and necessary—they need work. Our cover story shows how CMS is still again tinkering with how it will pay for palliative are and hospice, so things could change again. But doctors don't need to wait for the perfect model to do the right thing, nor should they. The perfect opportunity to do the right thing is never far away. ◆

Sincerely,

Mike Hennessy, Sr
Chairman and Founder

CONTENTS (CONTINUED)
APRIL 2020, Volume 26, Issue 4

Jeffrey Lowenkron, MD, MPP, Chief Medical Officer, The Villages Health, Florida, said that most seniors know what they want to do regarding advanced care planning, but their primary care physicians do a poor job of talking to them about it. The only physician group that does a worse job, he said, are oncologists.

PHOTO © ANDREY ARKUSHA / ADOBE STOCK

CONTINUED FROM SP102

SP118-SP119

Medical World News®

POLICY UPDATE

Oncology Care First Is a Big Step Toward Bundled Payments in Cancer Care, Authors Say

CLINICAL UPDATES

Novel Blood Biopsy Detects MRD in Early-Stage Breast Cancer

Study Examines Fixed-Duration Therapy in Patients With MM Ineligible for Transplants

TARGETED THERAPY

New Study Offers First Direct Comparison Between Venetoclax, Ibrutinib in CLL

SP122-SP123

AJMC TV

PRODUCED BY GIANNA MELILLO

Jeffrey Lowenkron, MD, MPP, Chief Medical Officer, The Villages Health

Maen Hussein, MD, Physician Director of Finance, Florida Cancer Specialists

Rebecca Kirch, JD, executive vice president, Health Care, Quality and Value, National Patient Advocate Foundation

Michael Diaz, MD, President of Community Oncology Alliance and Assistant Managing Physician at Florida Cancer Specialists

Lucio Gordan, MD, President & Managing Physician, Florida Cancer Specialists

Biosimilars May Help Bridge the Transition From Fee-for-Service to Value-Based Care

Healthcare Providers Are Feeling the Burden of Rising Costs

Financial challenges remain the #1 concern of hospital executives according to the 2018 American College of Healthcare Executives' annual survey.[1] Similarly, oncology practices face significant financial strain, which has resulted in over 1600 community oncology practice closures, hospital acquisitions, and corporate mergers in the past decade.[2]

One way to alleviate this burden is through utilizing opportunities to recognize cost savings. For example, hospitals may be able to leverage cost savings to reallocate funds for other important projects not funded by Medicare or commercial payers. In addition, this may lead to better management of hospital budgets to optimize care and a positive budget impact on drug spend for hospital inpatients.[3]

The Healthcare Industry Is Feeling the Effects of the Shift to Value-Based Care

In recent years, there has been a significant transition in focus from fee-for-service to value-based care. The goal of a value-based care system is to encourage clinicians to provide quality and efficient care, as well as improved outcomes at a lower cost.[4]

There have been several actions in the market place to recognize this shift to value-based care. For example, the Centers for Medicare & Medicaid Services (CMS) has created value-based care programs that reward providers with incentives for lowering costs and improving the quality of care they provide to Medicare beneficiaries. An example of this type of market reform is the development of a voluntary pilot program called the Oncology Care Model (OCM), which is designed to test the effects of improved care coordination, greater access to practitioners, and appropriate clinical care on both health outcomes and the cost of care for patients receiving chemotherapy.[5] Another type of market reform that was recently announced, the Patient-Centered Oncology Payment (PCOP) model, offers a way to expand on the OCM experience and represents an additional step towards innovation.[6]

This shift from fee-for-service to value-based care is playing a significant role in how practices and providers are viewing the cost of care.[8]

IN LIGHT OF THESE MARKET TRENDS

87% **of community oncologists surveyed are thinking differently about drug choices as a result of value-based care.[9]**

In order to manage appropriate utilization and take more risk, it will be crucial to assess the expense side of the equation as well.[10]

As the industry shifts to value-based reimbursement models, healthcare systems will continue to realize the need for solutions that advance health initiatives and support quality care objectives in the future.[7]

References:

1. American College of Healthcare Executives. Top issues confronting hospitals in 2018. https://www.ache.org/learning-center/research/about-the-field/top-issues-confronting-hospitals/top-issues-confrontinghospitals-in-2018. Accessed November 1, 2019. **2.** Chartis Oncology Solutions. Optimizing your oncology practice: real-world approaches that produce results. https://www.chartisforum.com/wp-content/uploads/2018/12/Oncology-WP-2018_FINAL-12-14.pdf. Published May 14, 2019. Accessed November 1, 2019. **3.** Data on file. Pfizer Inc., New York, NY. **4.** Bean M. Two-sided risk is coming – here's how healthcare providers can prepare. https://www.beckershospitalreview.com/payer-issues/two-sided-risk-is-coming-here-s-how-healthcareproviders-can-prepare.html. Published October 2, 2017. Accessed November 1, 2019. **5.** Centers for Medicare & Medicaid Services. OCM performance-based payment methodology. https://innovation.cms.gov/Files/x/ocm-pp3be-yond-pymmeth.pdf. Published December 17, 2018. Accessed December 1, 2019. **6.** ASCO. ASCO launches new payment reform model to transform cancer care delivery and enhance the quality of patient care. https://www.asco.org/about-asco/press-center/news-releases/asco-launches-new-payment-reform-model-transform-cancer-care. Published November 26, 2019. Accessed December 5, 2019. **7.** Walker T. The future of value-based care. Managed Healthcare Executive. https://www.managedhealthcareexecutive.com/news/future-value-based-care. Published November 1, 2019. Accessed December 5, 2019. **8.** The Deloitte Center for Health Solutions. The great consolidation: the potential for rapid consolidation of health systems. https://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-scienceshealth-care/us-lshc-great-consolidation-111214.pdf. Published 2014. Accessed November 1, 2019. **9.** IntegraConnect. How is value-based care changing cancer treatment decisions? http://campaign.integraconnect.com/vbc-oncology-survey. Accessed December 1, 2019. **10.** HealthLeaders. Value-based care is ripping into health system profits. https://www.healthleadersmedia.com/finance/value-based-care-ripping-health-system-profits. Accessed December 2, 2019. **11.** Centers for Disease Control and Prevention. Understanding value-based insurance design. https://www.cdc.gov/nccdphp/dch/pdfs/Value_Based_Ins_Design.pdf. Accessed July 15, 2019. **12.** NEJM Catalyst. New Marketplace Survey. Transitioning payment models: fee-for-service to value-based care. https://catalyst.nejm.org/transitioning-fee-for-service-value-based-care/. Accessed December 3, 2019. **13.** Community Oncology Alliance. COA biosimilars position statement. https://www.communityoncology.org/biosimilars-community-oncology-alliance-position-statement/. Accessed on December 3, 2019. **14.** Patel KB, Arantes LH Jr, Tang WY, et al. The role of biosimilars in value-based oncology care. *Cancer Manag Res.* 2018;10:4591-4602. **15.** Strober BE, Armour K, Romiti R, et al. Biopharmaceuticals and biosimilars in psoriasis: what the dermatologist needs to know. *J Am Acad Dermatol.* 2012;66(2):317-322. **16.** Scheinberg MA, Kay J. The advent of biosimilar therapies in rheumatology—"O brave new world." *Nat Rev Rheumatol.* 2012;8(7):430-436. **17.** Henry D, Taylor C. Pharmacoeconomics of cancer therapies: considerations with the introduction of biosimilars. *Semin Oncol.* 2014;41(suppl 3):S13-S20. **18.** US Food and Drug Administration (FDA). Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Silver Spring, MD: FDA; April 2015.

Unlocking the Potential of Biosimilars

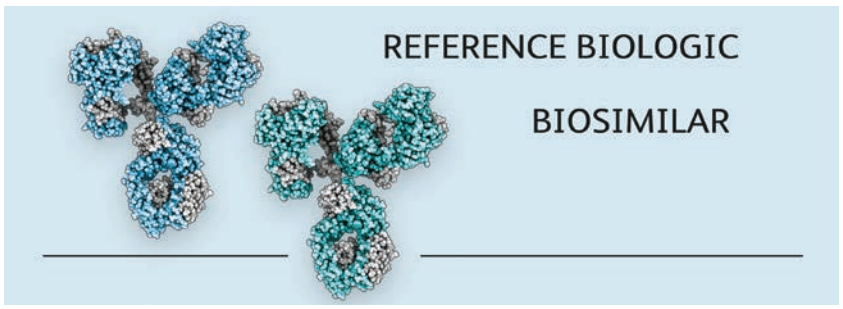
Given the growing costs of cancer care, delivering value while maintaining efficacy and safety is a pivotal issue in today's healthcare environment. Biosimilars may help address this issue by providing additional treatment options, at a potentially lower cost, while providing highly similar safety and efficacy to their reference biologic.[11-13] They may potentially better position providers for emerging value-based care initiatives from payers and employers through availability of lower-cost treatment options resulting in reduced drug spend. In addition, biosimilars may help meet established cost targets and position for future risk-sharing for OCM practices.[13-14]

Biosimilars May Prove Fundamental to the Future of Oncology Care, as We Shift to Value-Based Care as a Solution to Contain Costs[15-17]

- By potentially reducing costs and helping decrease financial risk in an emerging value-based environment, biosimilars may be able to unlock resources that can be reinvested in improving patient care
- Biosimilars may potentially offer a variety of therapeutic options at a lower cost, as well as savings and efficiencies for the healthcare system
- Demonstrating the ability to lower costs for high volume, costly therapies may prove beneficial with practice discussions with payers

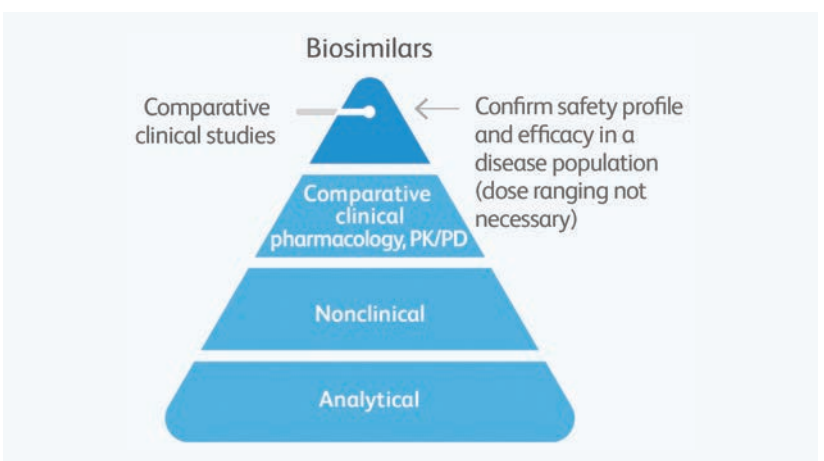
Introduction to Biosimilars

- A biosimilar is a biologic medicine that is highly similar to a reference biologic, with no clinically meaningful differences in terms of safety, purity, and potency[18]
- As potential alternatives to reference biologics, biosimilars may potentially expand treatment options and lower costs to meet the growing demand for biologic therapies



Development and Approval of Biosimilars

Extensive analytical, clinical, and nonclinical studies are part of biosimilar development[18]



The FDA approval process evaluates the totality of evidence to help ensure biosimilar quality, efficacy, and safety[18]

- A comparative clinical study is typically required to confirm no clinically meaningful differences between the 2 products
- Comparative human pharmacokinetic/pharmacodynamic (PK/PD) studies and clinical immunogenicity assessment are expected
- Nonclinical testing to evaluate the toxicity and safety profiles of the biosimilar is required
- Robust analytical testing, including comparative structural and functional characterization, is performed

For more information, please visit PfizerBiosimilars.com

Pfizer Oncology

BOOK REVIEW

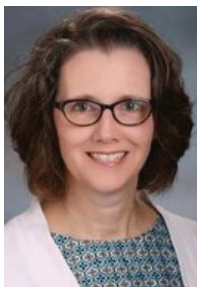
One Oncologist's Journey With a Patient to the Outcome We All Face

Patel, Kashyap. Dying Without Fear: The Pursuit of Eternity. *Penguin Random House India; 2020.*

Reviewed by Florence Caffrey Bourg, PhD

PATEL

Kashyap B. Patel, MD, is a medical oncologist and hematologist who serves as chief executive officer of Carolina Blood and Cancer Care Associates in Rock Hill, SC.



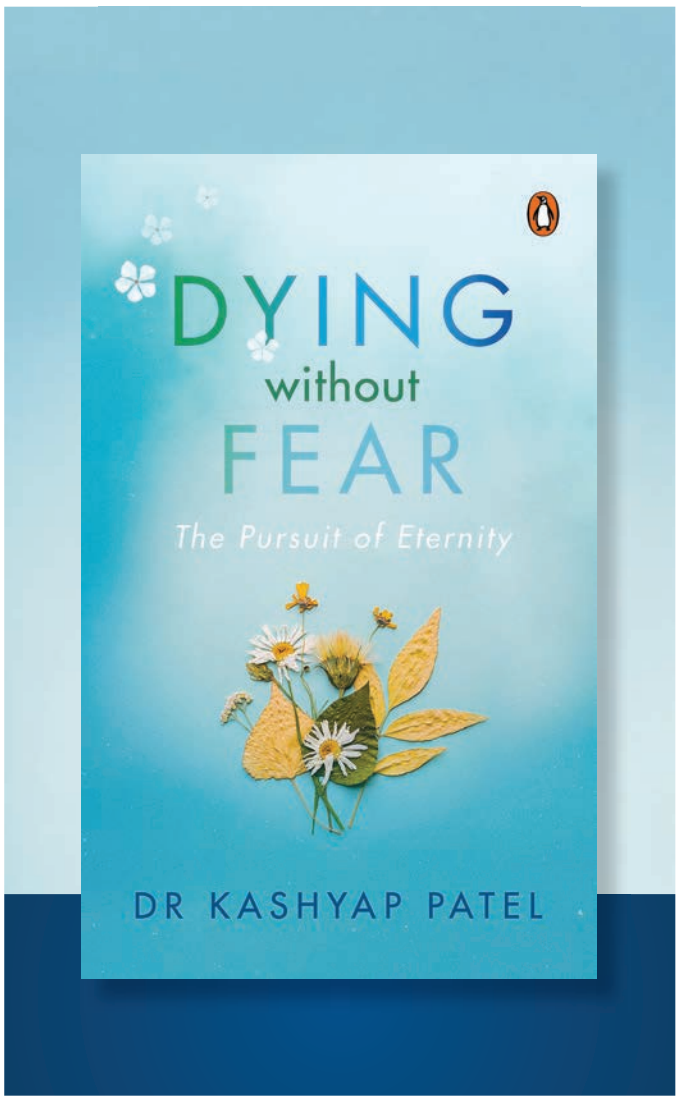
BOURG

Florence Caffrey Bourg, PhD, is an adjunct faculty member in the Loyola Institute for Ministry, New Orleans, LA, where she has developed coursework for ministries, including hospital chaplaincy. She received her PhD in theology, with specialization in ethics, from Boston College.

"Help me. I've never seen death before. Tell me what you know about it; what you've seen. What was it like to witness your patients leaving this world? Tell me how you coped with it. Aren't you afraid of death yourself? … Can I prepare for my own death? Can I prepare my dear wife and daughters? … I need to know what happens when people die. I'd like to know so that I can plan my own exit. I want to go away in celebration, not gloom." …

"Yes, I can definitely share my journey with you. I will also share some of my other patients' stories with you, if you believe they will help.…When do you want to begin?"

"Maybe we can meet once a week at lunch time, here under this beautiful copper dome. Could we start tomorrow?"



SO BEGINS A SERIES of conversations which unfold in the captivating relationship between Harry Falls, a former pilot with the British Royal Air Force and later a flight instructor in the United States, and Kashyap Patel, MD, author of *Dying Without Fear*, which will be available soon from Penguin Random House India. Production delays due to coronavirus disease 2019 will require the April 2020 launch date to be rescheduled.

Readers of *Evidence-Based Oncology*™ (*EBO*) will recognize Patel as an associate editor and contributing author. Patel is a medical oncologist/hematologist and the chief executive officer of Carolina Blood and Cancer Care Associates, based in Rock Hill, South Carolina. Having grown up in India and practiced medicine on 3 continents, he has devoted tremendous personal time and travel to nourish his interest in world religions and cultures—particularly to gain insight into the universal human experience of death.

Falls, married to one of Patel's colleagues, died within months of a diagnosis of lung and liver cancer. Yet, amid the challenges of his illness, Falls was incredibly fortunate. He had the rare opportunity to discuss his questions about death with Patel, a physician and friend who was exceptionally well-equipped to help Falls prepare for what the aviator called his "ultimate and infinite journey." Throughout the last months of Falls' life, the pair met weekly to examine death from multiple vantage points: physical, emotional, relational, cultural, and spiritual–religious–philosophical. Their encounters provide the foundation of *Dying Without Fear*.

Patel's medical facility was well-designed for conversations with Falls. The doctor explains, "My clinic, Carolina Blood and Cancer Care, was founded on a holistic approach to the treatment of cancer. We constructed the building with a U-shaped design that allowed all patients to look out onto a healing garden with a gazebo topped by a golden dome. When weather permitted, patients could receive their chemotherapy treatments outside on the patio or under the dome. It wasn't just for the patient's comfort. During difficult discussions, a quick glance at the garden in bloom or the smile of a patient resting in the sun grounded me, put life in perspective, and reminded me of my mission of service." Patel's clinic was an early adopter of the patient-centered cancer care model designed to serve holistic needs of patients, with a focus on palliative care.[1] As described previously in *EBO*, Carolina Blood and Cancer Care Associates has been one of the most successful practices in the country in executing alternative payment models (APMs), which gives practices more support to help patients with advanced care planning.[1,2] But when Patel and Falls were having their conversations years ago, these ideas were still new, and support systems like the one that Patel created for Falls were harder to find.

The healing garden is the recurring setting where readers of *Dying Without Fear* will vicariously accompany Falls along his journey toward death. Pondering his grim diagnosis, Falls decides not to pursue chemotherapy or any other treatments, because they would involve difficult adverse effects and would be unlikely to prolong his life significantly. "After evaluating where I stand and how I've lived all these years, I feel it would be best for me to

start packing my bags for the ultimate and infinite journey. … God blessed me with a life that I have no regrets over … Let's face it, Doc. From everything you've told me, treating my cancer is like trying to save an exploding plane in mid-air. Chances are it's not going to happen. … I think of it like I've just received an upgrade on a long flight. I've collected so many miles that God has granted me a charter flight to a destination unknown. Now the only issue is the waiting time."

Doctors have debated for more than 20 years on how to engage cancer patients in the decision-making conversation once they have reached the terminal stage.[3] The culture of care in the United States suggests that Falls is an exception, with language around treatment calling on patients to "fight" cancer even when it cannot be cured. A 2019 study of 20 women with metastatic breast cancer found that "patients' definition of a good compassionate doctor was one who gives positive news and leaves room for hope."[4] Another study published last year found that 28% of patients with imminently fatal colorectal cancer received treatment, even though this can prevent palliative care.[5]

Patel writes, "Even when I was seeing patients with very advanced cases where I knew they were better off dying peacefully than going through the pains of chemotherapy, which bought them maybe a few more weeks, almost every patient I came across was adamant about hoping for a miracle. But Harry was different."

Falls decides he will not pursue extraordinary measures to avoid death, but he has an extraordinary curiosity about the dying process, which Patel strives to appease. Upon receiving his terminal diagnosis, Falls says, "Doc, I'm not a religious or ritualistic individual. I'm somewhere between a non-believer and an agnostic. But I have some fundamental existential queries that are haunting me. … I want to know how death has been defined all these millennia. How do people die? Did our ancestors understand death in a similar fashion to our understanding? How did they treat the bodies after death? How was this different across cultures? What about the afterlife? What is a good death, or rather, what does it mean to die well? I can handle a mid-air somersault and navigate the worst turbulence. But I am totally incapable of even remotely imagining my own mortality and afterlife."

Patel responds, "I wish everyone facing death, which is in fact everyone someday, would spend time thinking about these questions."

Patel comes to the conversations with immense cross-cultural knowledge. The reader is drawn in by poignant stories of a doctor and his terminal cancer patients, which stimulate Falls' discernment about how to spend his final days meaningfully, and about disposition of his body after death. For example, Patel introduces the Indian custom of a funeral pyre, and describes how he fulfilled the traditional ceremonial role of igniting his brother's funeral pyre. He explains beliefs and rituals associated with death in ancient Egypt, Greece, Rome, and Australia, and in Hinduism, Buddhism, Judaism, Catholicism, evangelical Christianity, and Islam. He delves into topics not normally covered in a physician's training, such as the human soul, possibilities for an afterlife, and the meaning of suffering.

Although his cancer is not cured, Falls satisfies his human need to prepare for a peaceful death. Readers will not want to put the book aside until they learn how Harry's story ends.

Patel's purpose for writing *Dying Without Fear*, described in an interview with *EBO*, is to prompt communal and personal preparation for a profound human experience that is unavoidable, yet—paradoxically—too seldom a subject of open conversation. Patel thinks humans will have more meaningful and comfortable experiences of death if their community does not treat death as a taboo subject, or an event to be delayed through extreme, often painful measures that yield meager improvement in longevity or quality of life. He writes:

> *"I see it every day; patients in their last few days enduring horrifically painful therapies when we have already informed them that the end result of that dreadful suffering will be maybe two or three more weeks of life spent in agonizing pain. The pain and the therapy do not allow them to spend time with their loved ones or enjoy the comforts of life. Those few weeks are spent chained to a hospital bed. We are too willing, it seems, to bargain away quality time with those we love and freedom from debilitating pain in exchange for fourteen to twenty-one more days on earth. And in that last leg of the marathon, instead of preparing and planning for a graceful and pain-free departure surrounded by those we hold dearest, we prefer to ruin those last, most precious moments in pursuit of a farfetched cure, ensuring that the final days we spend on earth are the most miserable of our entire lives. It is this fate that, as a physician who has been at the deathbed of countless numbers of my patients, I want to help people avoid."*

As Patel shares stories of his deceased patients, it's evident that they have benefited from a highly attentive physician. He accepts their calls to his cell phone at all hours; he visits their homes; he attends their funerals. Readers who have struggled to schedule appointments with their physicians may be astonished at the generosity of the time spent with Falls. Yet, from an ethical perspective, *Dying Without Fear* raises serious systemic concerns about empowering patients to exercise genuine informed consent. How much is informed consent for end-of-life decisions undermined—or impossible—for countless patients who begin the dying process as Falls did, but never have the opportunities for education and reflection that he received?

Like Harry Falls, many patients, caregivers, and medical professionals lack guidance or opportunity to prepare existentially for the dying process before they are thrust into it. In the era of quality metrics in healthcare, the HealthCare Chaplaincy Network has developed a measure for comprehensive palliative care that includes relief of existential or spiritual distress, which can be as burdensome as physical pain.[6] Guidelines from both the National Comprehensive Cancer Network[7] and the Healthcare Chaplaincy Network call for palliative care to begin well before a terminal patient is admitted to hospice care. Patel has previously published critiques of the medical profession's insufficient training for managing the holistic needs of dying patients.[8] In *Dying Without Fear*, he says, "End-of-life discussions are the most difficult part of my job"; yet, repeatedly, he states that nothing in his medical school training prepared him for this role.

That structured medical education largely neglects end-of-life-discussions might be considered tolerable for physicians who are less responsible for delivering terminal diagnoses—but certainly not for an oncologist. In the interview with *EBO*, Patel was asked whether skills for conducting end-of-life-discussions can be effectively taught to medical professionals. Patel said he thinks that improvements in structured training are certainly possible and much needed. He has sought this training for himself—for example, by becoming a certified trainer of physicians through the Education in Palliative and End-of-Life Care program affiliated with Northwestern University's Feinberg School of Medicine.[9]

Mindful of the losses Patel has endured with his dying patients, Falls and other characters in *Dying Without Fear* ask him questions such as, "Doc, how do you keep doing this?" … "Don't you ever get burned out … from doing this over and over again?" … "Does dealing with death not affect you, your personal life?" Research indicates that these are precisely the sorts of questions medical professionals should be taking seriously. Burnout, trauma, posttraumatic stress disorder (PTSD), depression, and struggles with work–life balance are more common in the medical profession than many realize.[10-12]

At several points in his book, Patel notes that professionals like himself are expected to "remain emotionally detached" or to "rein in [their] personal emotions" when engaging with patients, but he "had never been fully successful" at doing so. But why should professional "success" be measured by the criterion of emotional detachment? Those who approach death from a more pastoral or therapeutic perspective will be concerned that medical professionals like Patel need healthy ways to process their human emotions. Patel admits to Falls, "As an oncologist it's always been my job to guide patients through their own grief. I can't burden people facing death themselves with my own sorrows at death's hands. I try not to burden even my own family and try to shelter even my dear wife from it. Sometimes, I wake up in the middle of the night questioning my own judgment about what I have learned. I should thank *you* … I rarely have an outlet for my own grief."

When asked about available resources to facilitate and de-stigmatize emotional supports for medical professionals who experience grief, depression, trauma, PTSD, or stress and exhaustion related to care for dying patients, Patel agreed that "a lot more could be done" in all these areas. In *Dying Without Fear*, Patel describes instances when he found himself tragically torn between special events with his family and untimely requests to tend to dying patients. On one occasion, when called to the »

bedside of a dying patient, Patel felt compelled to cancel plans to attend the wedding of a daughter of one of his best friends. He asks for forgiveness from his wife who is left to attend the wedding alone. While these struggles are not unique to the medical profession, mission-driven medical providers in high-stress roles should have supportive employment structures that allow them to maintain their physical, emotional, and spiritual health—which Patel's practice has pursued with a team-based approach, supported with APMs.

Dying Without Fear is an accessible narrative that will be marketed for broad readership. Patel writes that he hopes this project will contribute to transforming cultural attitudes and institutions, such that planning for "a smooth, graceful and celebratory death and departure" is no more unusual or taboo than preparation for birth. This book is an excellent choice for professional development and personal enrichment. Beyond obvious audiences, such as medical professionals, grief therapists, and chaplains, it could be a powerful selection for community book clubs, or as an interdisciplinary shared reading assignment for first-year university students. Patel models a mature level of interdisciplinary, cross-cultural, and interfaith literacy which, ideally, should be more the norm than the exception. To reach the broadest possible audience, *Dying Without Fear* could be transformed into an outstanding theatrical production or screenplay—with the healing garden at center stage. ◆

AUTHOR INFORMATION

Kashyap B. Patel, MD, is a medical oncologist and hematologist who serves as chief executive officer of Carolina Blood and Cancer Care Associates in Rock Hill, SC. He is a national leader in clinical trials, precision medicine, the use of biosimilars, state and federal legislative affairs, and healthcare management. Patel has been an independent contractor for Palmetto GBA and currently serves as vice president of the Community Oncology Alliance and as a trustee of the Association of Community Cancer Centers.

REVIEWER INFORMATION

Florence Caffrey Bourg, PhD, is an adjunct faculty member in the Loyola Institute for Ministry, New Orleans, LA, where she developed multimedia materials and the course textbook for Spirituality, Morality, and Ethics, a required course for graduate and certificate students training in the LIM program for various ministries, including hospital chaplaincy. She received her PhD in theology, with specialization in ethics, from Boston College, and is the author of *Where Two or Three Are Gathered: Christian Families as Domestic Churches* (University of Notre Dame Press, 2004).

REFERENCES

1. Patel K, Patel M, Gor A, et al. Oncology practice transformation helps deliver patient-centered cancer care in a community oncology practice. *Am J Manag Care*. 2018;24(5 Spec No):SP147-SP148.
2. Patel K, Patel M, Lavender T, et al. Two-sided risk in the Oncology Care Model. *Am J Manag Care*. 2019;25(6 Spec No):SP216-SP220.
3. Asai A. Should physicians tell patients the truth?. *West J Med*. 1995;163(1):36-39.
4. Bergqvist J, Strang P. Breast cancer preferences for truth versus hope are dynamic and change during late lines of palliative chemotherapy. *J Pain Symptom Manag*. 2019;57(4):746-752. doi: 10.1016/j.jpainsymman.2018.12.336.
5. Sineshaw HM, Jemal A, Ng K, et al. Treatment patterns among de novo metastatic cancer patients who died within 1 month of diagnosis. *JNCI Cancer Spectr*. 2019;3(2):pkz021. doi: 10.1093/jncics/pkz021.
6. What is quality spiritual care in healthcare and how do you measure it? website. healthcarechaplaincy.org/docs/research/quality_indicators_document_1_16_2020.pdf. Published January 16, 2020. Accessed March 24, 2020.
7. Dans M, Smith T, Back A, et al. NCCN Guidelines Insights: Palliative Care, version 2.2017. *J Natl Compr Canc Netw*. 2017;15(8):989-997. doi: 10/6004/jnccn.2017.0132.
8. Patel K, Kruczynski M. Palliative and end-of-life care: issues, challenges, and possible solutions in the United States. *Am J Manag Care*. 2015;21(6):SP195-SP196.
9. Home page. Center for Bioethics and Medical Humanities at Northwestern University website. bioethics.northwestern.edu/. Accessed March 24, 2020.
10. Lazarus A. Traumatized by practice: PTSD in physicians. *J Med Pract Manage*. 2014;30(2):131-134.
11. Jackson TN, Morgan JP, Jackson DL, et al. The crossroads of posttraumatic stress disorder and physician burnout: a national review of United States trauma and nontrauma surgeons. *Am Surg*. 2019;85(2):127-135.
12. Cooper B, DeVries J. Promoting staff well-being and success: a work-life balance team initiative. Health Care Chaplaincy Network website. healthcarechaplaincy.org/caring-for-the-human-spirit-presentations/conference-2018-presentations.html. Presentation at: 5th Annual Caring for the Human Spirit Conference; April 23-25, 2018; xx, xx. See also collected resources on stress and burnout in the medical profession at Stanford Medicine's WellMD website: wellmd.stanford.edu/healthy/stress.html.

In Florida, Serving the Senior Population in Oncology Means Working Together

Mary Caffrey

THE ELBOW BUMPS SHARED at the Tampa Hilton Downtown on March 5, 2020, foreshadowed what was to come: this would be the last large gathering for a while at which oncologists from across Florida Cancers Specialists (FCS) would be able to join with physicians and other stakeholders for a strategy session on what this group does best: bringing value to cancer care.

"Quest for Value: Advancing Oncology Value-based Care," this year's first installment in the Institute for Value-Based Medicine (IVBM) from *The American Journal of Managed Care®*, zeroed in seniors, a population that's growing not just in Florida but across the United States. US Census Data show that by 2030, about 1 in 5 Americans will be 65 years or older.[1] Older Americans are more likely to develop cancer, but thanks to better detection and treatment, they are more likely to survive cancer, too.

If everyone has a better than 1 in 3 chance of developing cancer in their lifetime,[2] then care for a senior with cancer is a shared responsibility. There's an oncologist and the primary care physician. There's the payer who enrolls the person in health plan, and there's the pharmacy that may see the patient the most—not just for prescriptions, but also for supplies, personal products, or a routine question.

All were represented at the Tampa event, which featured:

- **Lucio Gordan, MD,** president and managing physician, FCS
- **Sam Asgarian, MD,** former head of Clinical Health Products and Services, CVS Health
- **Ray Parzik,** director of Network Programs, Florida Blue
- **Jeffrey Lowenkron, MD, MPP,** chief medical officer, The Villages Health
- **Michael Diaz, MD,** assistant managing physician, FCS; president, Community Oncology Alliance
- **Maen Hussein, MD,** physician director of finance, FCS

Gordan opened the discussion by introducing the classic definition of value: quality divided by cost. But he explained that value can be subjective, because, "It depends on who the stakeholder might be."

When one thinks of "value" like a pie, and the slices must be shared among the physician, the payer, the pharmaceutical company, and the pharmacy benefit manager (PBM), then "it gets very tricky," he said.

FCS is among the leading practices in the nation figuring out how to navigate this new territory in oncology care, as it has been working with value-based payment even before CMS' Oncology Care Model (OCM) existed. Making value-based reimbursement work requires collaboration with others in the healthcare landscape who interact with the patient, so that information is shared. Learning how to enhance provider-to-provider communication creates "a new culture of sustainability," Gordan said.

Top Down Commitment

So, how did Florida Blue get to the point of collaborating with FCS on its Community Oncology Model? Parzik shared the timeline for the process and struck a theme heard often at IVBM sessions: without leadership from the top, the shift to value-based care does not happen.

"It takes top down commitment," Parzik said, describing the process that began in 2010 with a pathways program and evolved from there, including an intense 6-month period of program development that emerged when a community oncology practice, a large hospital system, and a large health plan decided to make the leap.

But bringing all the parties together—to get the technology and the electronic health records to interact—mattered. Within a few years, Florida Blue had set up an accountable care organization. That mattered as the plan prepared for the arrival of the Affordable Care Act (ACA). "Florida Blue was in all 67 counties when the ACA went live, and we're still successful," Parzik said.

But what led the payer to do an oncology-based model? "It's the most difficult thing to try to measure," he said. Cancer has different stages, patients have different genetics, and administrative claims data don't reveal all that. "How do you marry clinical analytics with financial analytics?"

"If this is a shared savings model, we don't want to have any financial transaction take place at the detriment of quality … We want to save money [through] care coordination."

—Ray Parzik,
Director, Network Programs
Florida Blue

Hence the other truism of value-based care: the physicians must buy in.

The current collaboration with FCS dates back to 2015-2016, when Florida Blue saw opportunities to work with the practice to run pilots and refine attribution models before they were used on larger groups. Getting it right is important, Parzik said.

What indicators are the most helpful?

"If this is a shared savings model, we don't want to have any financial transaction take place at the detriment of quality. … We want to save money [through] care coordination."

There's a big difference today from the first generation of managed care, he said. Payers have learned that squeezing the provider to the point that the provider cannot succeed makes no sense. "If people are not succeeding, it's not sustainable," he said.

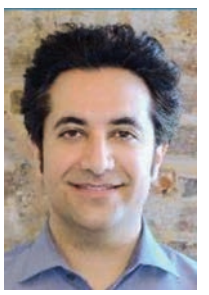
Value-Based Decisions on Therapy

Asgarian presented details of the Novologix platform, which CVS Health developed to act as a built-in "second opinion" to deploy value-based contracting and speed prior authorization of cancer therapies.

"Why did we start with oncology?" he asked rhetorically. "There is great differentiation compared to what else is out there."

Things like the National Comprehensive Cancer Network (NCCN) guidelines act as a built-in check against prescribers going astray, and the top-tier providers in each area of cancer are well known. So, Asgarian said, the idea was to take Novologix, »

GORDAN
Lucio Gordan, MD; President & Managing Physician, Florida Cancer Specialists (FCS)



ASGARIAN
Sam Asgarin, MD; Former Head of Clinical Health Products and Services, CVS Health

PARZIK
Ray Parzik; Director of Network Programs, Florida Blue

LOWENKRON
Jeffrey Lowenkron, MD, MPP; Chief Medical Officer, The Villages Health

DIAZ

Michael Diaz, MD; Assistant Managing Physician & President of COA, Florida Cancer Specialists (FCS)

HUSSEIN

Maen Hussein, MD; Physician Director of Finance, Florida Cancer Specialists (FCS)

which was created as a drug platform, and turn it into a treatment decision support platform.

By integrating the platform with NCCN guidelines, genetic information, and information from care managers, and guideline customization, Asgarian said, the goal is to "not just treat the cancer but treat the individual."

Where the Seniors Keep Coming

With 130,000 people, The Villages is the size of a city. It has 3 town squares, thousands of social clubs, music every night, and "more baseball games than Major League Baseball," according to Lowenkron, the person tasked with keeping them all healthy.

Living up to the moniker, "America's Healthiest Hometown," is no small order, but The Villages Health embraces it uniquely. In a place where the average age is 70, there are 100,000 people eligible for Medicare, so it makes sense for CMS to work with Lowenkron to get it right.

Seniors end up with fragmented care because Medicare historically will not pay for a longer appointment where specialists all come to the patient in a single setting, but CMS will pay for multiple 15-minute visits. The Villages in Florida is trying to address this with CMS because 100,000 people who live there are enrolled in Medicare.

If people wonder why care is fragmented, he said, historically Medicare would not pay for an extended visit in which various specialists would come to the patient. But if the patient made separate, 15-minute appointments, "they pay everybody!"

Gone are the days when a person got sick and went "to the airport," he said. The Villages now has multiple care sites, anchored by its own hospital and a 285,000 square foot, 5-story ambulatory health center, hotel, and spa complex. Specialty offices for oncology and ophthalmology are on site, and family members can stay nearby. Lowenkron said The Villages is very careful to evaluate which services it will provide and which ones are already available in the area, so it does not create more supply in the market than can be naturally absorbed. Careful collaboration with FCS and other providers ensures the right amount of care.

By taking these steps, "Our ER use is relatively low," Lowenkron said.

Where Things Could Improve

Hussein and Diaz joined the panel discussion that followed, where talk turned to the need for primary and oncology care to do a better job of coordinating on advanced care directives. "It's an incredible challenge," Lowendron said. He admitted that even though seniors have thought about it "84% of the time," primary care doctors don't ask often enough.

"Only one group is worse. We are among you all today," he said.

Diaz addressed rising drug costs and how they affect the senior population—as well as oncology practices as they take on risk. Stop loss is handled so that no one individual physician or office absorbs an outlier, which is better for patient and provider alike. Hussein, wearing his finance hat, said The Villages and FCS treat many of the same patients, and have "reached a middle ground to share incentives."

Other topics included the future of PBMs in the era of vertical integration: would they survive, and if so, how many? Were they even necessary?

Diaz, in his role with COA, discussed the future of OCM 2.0, an alternative payment model the group developed as a different way to reimburse practices for drugs, which has been a chief source of complaints about the CMS model—Gordan has published research showing that practices are being shortchanged under the current system.

Parzik addressed the topic of site parity—also a key issue for community oncologists, who say that reimbursement structures favor hospitals at their expense, even though they deliver care more efficiently. Hospitals, Parzik said, "always carry leverage," due to their impact on the community. "How do you fix that?"

He called for "creating preferred partnerships, with structured benefits with your membership." As prices become more transparent, the cost-saving sites will gain. He sounded much like a consumer when he said, "It's very difficult to shop for healthcare." Payers prefer discounts backed by evidence—competitive intelligence—that they have an actual impact on care.

"There's a whole host of models in the delivery system that are somewhat perverse," Lowenkron said. "I can never explain why they should be that way. …

"No one is going to raise their hand and say, 'I think I'm a little overpaid.'" ◆

REFERENCES

1. Colby SL, Ortman JM. Projections of the size and composition of the US population: 2014 to 2060. Current Population Reports, P25-1143, US Census Bureau, Washington, DC, 2014.
2. Siegel RL, Miller KD, Ahmedin J. Cancer statistics 2019. CA: A cancer journal for clinicians. doi.org/10.3322/caac.21551.

Reporting by Maggie L. Shaw

Thinking Outside the Box to Elevate, Increase Access to Cancer Care

EVOLUTION. DISRUPTION. INNOVATION. TELEMEDICINE. A virtual exchange of information. Healthcare has lagged behind in these aspects, but it is necessary to transcend time and distance, according to Susan Dentzer, senior policy fellow at the Duke-Margolis Center for Health Policy, during her presentation "Disruptive Innovations That Could Change the Delivery of Cancer Care" at the Association of Community Cancer Centers 46th Annual Meeting and Cancer Center Business Summit, held March 4 to 6 in Washington, DC. This is her vision for the future of cancer care.

Dentzer spoke passionately about elevating the quality of cancer care delivery by changing the system and asking these questions:

- How do we take the possibilities that exist and expand them?
- What are the best ways to innovate?
- What if, instead of a sick-care system, we had a healthcare and health-inducing system that went to the people rather than the people going to it?
- Why is this deemed necessary?

Her biggest question of all: for healthcare that mainly involves exchanges of information, not the laying on of hands, why isn't more of it done virtually today? This is especially pertinent when study results show high levels of patient satisfaction, higher quality of life, less depression, and less stress with telehealth and teleoncology.

DENTZER

According to Dentzer, it is time to think outside the box, incorporating data and technology to elevate cancer care delivery. She provided a telling question from A. Mark Fendrick, MD, coeditor-in-chief of *The American Journal of Managed Care*®, that illustrates how despite advancements in cancer care, obstacles to optimizing its delivery remain: "Why do we have Star Wars medicine on a Flintstones delivery platform? Shouldn't we at least advance to The Jetsons?"

What many do not realize is that telemedicine, at least the idea of it, has been around since the late 1960s. During her presentation, Dentzer related how Kenneth D. Bird, MD, a former internist and pulmonary specialist at Massachusetts General Hospital (Mass General), developed the first telemedicine system between Logan Airport and Mass General in 1968, with a second link in 1970.[1] However, the system was abandoned in the 1970s.

A common theme that ran throughout her presentation was that it is time for healthcare and cancer care to move outside the conventional walls of practices, to not be afraid of innovation, to move closer to patients where they are in their homes and communities. The quality of cancer care needs to be elevated to such a level that it minimizes the amount of time people have to be in the hospital. But doing so first means addressing several important challenges:

- An estimated 70% of US counties lack an oncologist.[2]
- There is an uneven distribution of the overall cancer labor force.
- The aging population has an increasing incidence of cancer.

So, what can we do? What are some examples of opportunities to innovate in medicine?

Teleoncology. This has already been shown to improve access to care and decrease costs, Dentzer noted. Also, with oral cancer drugs and immunotherapies being delivered on an outpatient basis in some instances, teleoncology can help by providing remote supervision of chemotherapy, thereby preventing unnecessary trips to the hospital or doctor's office.

For example, Boston University's Biomedical Optical Technologies Lab (BOTLab) has developed a wearable probe, now in clinical trials, that uses near-infrared spectroscopy to measure hemoglobin, metabolism, water, and fat levels in tumors. The University of Arizona created its telemedicine program in 1996 and introduced telemammography between rural locations and the university in the early 2000s; women's images from a remote location are analyzed *within 45 minutes* at the university. Lastly, in 1995, Kansas University Medical Center instituted its first teleoncology program with a multidisciplinary team that is 250 miles from a rural medical center, which itself has nurses.

Telegenetics. Abramson Cancer Center in Philadelphia, Pennsylvania, offers genetic counseling in real time, which can be accessed over the phone or through video conference. As this is a service that is not always easy to access, especially when patients are hundreds of miles away, making the counseling more portable can only serve to increase access to care.

Symptom management. Because not all patients need to be seen in the clinic, Seattle Cancer Care Alliance provides a web portal through which they can enter symptoms. This sends an alert to their care team and that alert leads to a phone call.

Provider education in immuno-oncology. This is particularly needed for emergency medicine physicians. Telemedicine can increase engagement and communication between experienced oncologists and emergency medicine physicians who may have limited knowledge of immunotherapies and their adverse effects. It also provides opportunities for online learning and 24/7 access to critical care information.

Access to clinical trials. Denzter pointed out that almost 8 of 10 clinical trials can be delayed, even closed, because recruitment takes too long. Telemedicine can remedy this by "expediting patients' access to clinical trials" through automated platforms.

"I would argue that the status quo is not an option. You need to take advantage of these capabilities really fast," Dentzer noted. ◆

REFERENCES

1. Dr Kenneth Bird, 73; used TV for diagnosis. *The New York Times*. nytimes.com/1991/02/16/obituaries/dr-kenneth-bird-73-used-tv-for-diagnosis.html. Published February 16, 1991. Accessed March 25, 2020.
2. Charlton M, Schlichting J, Chioresco C, Ward M, Vikas P. Challenges of rural cancer care in the United States. *Oncology (Williston Park)*. 2015;29(9):633-640.

Healthcare Needs Bipartisan Support to Benefit Patients, Stabenow Says

BEFORE HER KEYNOTE ADDRESS "A Frank Conversation About the State of Healthcare in the United States" during the Association of Community Cancer Centers' 46th Annual Meeting and Cancer Center Business Summit, held March 4 to 6 in Washington, DC, Senator Debbie Stabenow (D, Michigan), was introduced by Dennis A. Cardoza, cochair of the Federal Public Affairs Practice and chair of the California Public Affairs Practice of Foley & Lardner LLP. He polled the audience with this question: In 2019, healthcare emerged as the top policy issue for Americans. What do you see as the number 1 driving force behind this crisis?

1. Access to services
2. Concerns over the cost of treatment on the individual level, high co-pays, deductibles, etc
3. Concerns over the cost to society as a whole
4. The "broken" healthcare system
5. Concerns over the quality of care being delivered

Stabenow, a member of the Senate Finance Committee and ranking member of its health subcommittee, followed with her perspective on the state of healthcare costs in the United States today, touching upon how each of the above choices affects healthcare affordability. She reinforced the importance of investing in the country, in public infrastructure, and in public health infrastructure, especially where oncology is concerned, because "it's about hope. It's about finding a path. It's about providing life-saving medications." »

She expressed concerns over the Trump administration's promotion of short-term insurance plans, from a coverage and treatment standpoint, that don't have to cover people with pre-existing conditions or that don't provide the basic coverage called for by the Affordable Care Act (ACA). They are "cheap," she said, and patients don't know if they are covered until they get sick, whereas under the ACA, preventive care is covered without a copay.


STABENOW

The Congress is trying to figure out how to not go backward, Stabenow noted, especially in the face of President Trump's proposed $1.6-trillion cut in future healthcare spending, and "we're going to work very hard to push back."

One example is by supporting robust efforts for community health centers and certified community behavioral health centers, because "we predominantly treat these areas not as real healthcare, through healthcare reimbursement, but through grants." Communities deserve structurally sound, high-quality care.

Stabenow also discussed the cost of vaccines and treatments, shining the spotlight on a recent $3-billion investment in research and vaccines that did not include language guaranteeing that if this research produced effective vaccines, they would be affordable when brought to market.

"The federal government should use its power to negotiate a price," she pointed out. "Keeping the quality high is not worth it if at the end Americans can't afford the medicine."

Insulin prices have climbed about 15 times in the past number of years, she said, stressing again that Americans must have access to affordable medications.

"For every one of us, healthcare is not political, it's personal, and we should all be coming together on every issue, on a nonpartisan basis, to do what we can to make things better, to improve access to care, to improve the quality of care, and to reduce costs," she concluded. "We can have a difference of opinion in how we approach things. That's how you get to the good decisions. But we need to not start from a political or ideological position, but from the position of how to make things work." ◆

Patient Care Must Be an Ongoing Collaboration That Includes Multifaceted Concerns, Panel Says

THE THEME OF the Association of Community Cancer Centers' immediate past president Ali McBride, PharmD, MS, BPS, BCOP, for his 2019-2020 term was "Collaborate. Educate. Compensate: A Prescription for Sustainable Cancer Care Delivery." Nowhere was that more evident than in the panel discussion he led on day 2 of this year's annual conference, which focused on the importance of supporting patients and not just managing the process of their care.

McBride, clinical coordinator, hematology/oncology, Department of Pharmacy, The University of Arizona Cancer Center, was joined on the panel by:

- **Al B. Benson III, MD, FACP**, professor of medicine, Division of Hematology/Oncology, Northwestern University Feinberg School of Medicine
- **Rebecca Kirch, JD**, executive vice president, Health Care, Quality and Value, National Patient Advocate Foundation
- **Barbara L. McAneny, MD, FASCO, MACP**, chief executive officer, New Mexico Oncology Hematology Consultants, Ltd; immediate past president, American Medical Association
- **Brenda Nevidjon, MSN, RN, FAAN,** CEO, Oncology Nursing Society
- **Randall A. Oyer, MD**, ACCC president-elect; medical director, oncology, Penn Medicine/Lancaster General Health, Ann B. Barshinger Cancer Institute
- **Melanie R. Smith, PharmD, BCACP, DPLA**, director, Section of Ambulatory Care Practitioners, Member Relations, American Society of Health-System Pharmacists
- **Lara Strawbridge**, director, Division of Ambulatory Payment Models, Center for Medicare and Medicaid Innovation

The panel discussed the results of Resource and Reimbursement Barriers to Comprehensive Cancer Care Delivery, an ACCC survey originally piloted at the 2018 and 2019 annual meetings that was meant to gauge barriers to delivering the most effective and comprehensive cancer care. Following the 2019 meeting, 172 ACCC member programs responded to questions that covered 27 supportive oncology services, and this panel touched on 5 of them:

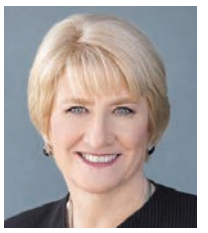
1. Patient navigation
2. Financial needs counseling and navigation
3. Palliative care services
4. Survivorship care planning
5. Clinical trials

McBride opened the discussion by relating that more than half of the responding oncology practices said they had inadequate resources to provide nutrition, palliative care, financial services, or even genetic counseling. Most offer some supportive oncology services, but these vary in capacity. What they all agreed on, however, was the need for adequate staffing "to deliver supportive oncology services to all patients who need them."


MCBRIDE

"We need to create a dissemination strategy to inform policy and oncology reimbursement," McBride emphasized. "There needs to be sustainable care delivery. How does your organization do this?"

The results? Through the survey, the members of the panel helped develop a tiered, comprehensive cancer care services matrix whose top 5 areas are those mentioned above and explained in further detail below. It addresses such questions as what else is needed to add and/or grow this service and what members of the multidisciplinary team can and/or should provide.


MCANENY

Patient Navigation

"Navigation is a service, not a job description. Every person a patient comes in contact with has the job of navigating the patient through that part. Navigation is a process that needs to be hardwired into every single member of a team," McAneny stated.

The panel agreed on the importance of patient navigation being a team effort.


BENSON

"The idea is that when you meet a patient," Benson noted, "you can link them with the appropriate person on the team. So start at the very beginning to identify what is important to that patient."

Cost is also a factor in this area, as there needs to be adequate funds for both the physicians and their patients.

"There needs to be clearly designated time and resources to each team member so they can do their job and it doesn't become unsustainable over time," Strawbridge added. "We must recognize the investment in staff and resources and provide rewards in the form of reimbursement."

Financial Needs Counseling and Navigation

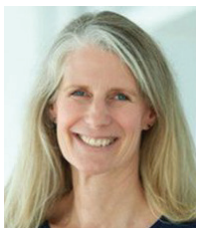
The survey results showed there is a gap between the cost and reimbursement of cancer care services, with out-of-pocket patient payments, grants, and charitable contributions making up the difference. However, often that is still not enough.


STRAWBRIDGE

"What is the return on investment?" McBride asked.

"Financial toxicity used to not be a thing," Kirch responded. "We must be amplifying the voices of what patients and their families need."

McAneny agreed, saying, "Even with Medicare, the out-of-pocket costs are enormous. It costs me $15 to collect the $5 copay. Look at the insurance industry. Stop playing the cost-shifting game. Two-thirds of bankruptcies are triggered by a medical event, and two-thirds of those have insurance."


KIRCH

Palliative Care

The overarching theme during this segment of the panel was that patients and their caregivers need to be heard and understood and that it is every care team member's responsibility. Patients can be educated on the role of palliative care, and comprehensive community cancer programs can develop and offer referral pathways.

Palliative care is not a one-time event; it continues throughout the cancer care process. Still, doctors do not want to have these conversations, Strawbridge pointed out.


OYER

"Patients with advanced lung cancer live longer with palliative care services," Oyer noted, "but only 19% are referred. Who needs to be educated? The patients or the system? We need a system that changes."

Kirch noted the reach of online training in this regard. "We need to train professionals. Start thinking how we can support these services. Everyone is responsible for providing palliative care to patients. Everyone needs to have basic conversations with patients about how treatment can impact lives."

"Nurses, pharmacists, physicians. It's everybody's job," Smith said. "It's an ongoing situation, not a fixed event." Nevidjon agreed, calling for an investigation into "what we are teaching in our education programs."


SMITH

Survivorship Care Planning

The panel agreed that survivorship care planning in oncology needs to be a dynamic process. The increasing numbers of survivors, over time, experience a lot of other comorbidities that the oncology community is not prepared to deal with, so primary care needs to be embedded with oncology, stated McAneny.

However, "primary care is in a crisis situation. In primary care, the shortage of providers is worse than in oncology. How do we handle 10 million patients and growing? What will be the long-term outcomes of people getting immunotherapy? This is one component of what we will need to do in the long run," Benson added.


NEVIDJON

"Patients groups remind us that they think of survivorship as starting when a patient is diagnosed," Strawbridge said.

Proposed solutions in the survey include providing a survivorship care plan to every patient and communicating this information to the patient's primary care physician (PCP). Again, collaboration was the name of the game, especially when working with PCPs on transfers of care and follow-up.

Clinical Trials

The panelists agreed that the current system needs updating because it is rife with issues. Major changes are needed. Oyer noted that the top 3 issues are staff resources, program infrastructure, and lack of patient understanding of the process, but that a solution is top of mind.

McAneny agreed that the system is flawed. "We need a system that opens trials in under a month. We need trial participants that more reflect the country we serve. It's a cumbersome and clunky system that desperately needs to be streamlined," she stated.

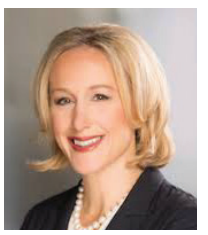
"We're constantly under pressure to make sure our populations include a diverse population. Patients want to be treated in the communities where they feel most comfortable. But those small local hospitals don't have the resources," Oyer responded. "We are going to develop a new roadmap on how to find a trial, so we can address the needs of traditionally [underserved] populations in our country."

"It's been a learning curve," McBride concluded. ◆

Clinical Decision Support Tools Transform Point-of-Care Delivery

"WE NEED WAYS TO BE better, to be more efficient. Can we predict which patients are at high risk of hospitalization, and how can we reduce this risk?" asked Debra Patt, MD, MPH, MBA, executive vice president of policy and strategy at Texas Oncology; medical director of analytics, McKesson Specialty Health; clinical professor, Dell Medical School, University of Texas at Austin; and editor-in-chief, *JCO Clinical Cancer Informatics*. "How many of you use clinical decision support systems that are integrated within your electronic health record to make therapy choices at the point of care? There's an opportunity to do better."

During her presentation "Applied Informatics in Oncology" at the Association of Community Cancer Centers 46th Annual Meeting and Cancer Center Business Summit, held March 4 to 6 in Washington, DC, Patt detailed Texas Oncology's experience using clinical informatics to guide treatment practices and decisions, which she believes can increase both the value and quality of care.


PATT

Using clinical informatics and decision support can help with guideline adherence, clinical and patient education, and predictive analytics. Having these tools helps to ensure quality by facilitating evidence-based decision making. This is especially important with the increasing numbers of long-term cancer survivors and the growing complexity of cancer care in regard to more cancer subtypes, treatments, combination therapies, and targeted treatments, especially immunotherapy, Patt pointed out.

Between 1991 and 2016, there was a 27% reduction in the overall cancer death rate, equating to more than 2.6 million lives saved, according to data Patt presented. And from 1971 to 2030, there is estimated to be a more than 7-fold increase—from 3 million to 22.1 million—in total cancer survivors.

"This is a totally different field than it was 10 years ago," Patt said. "When you have complexity, it's useful to have something like decision support to help you manage the complexity."

She emphasized that in order to be successful, these integrated solutions need to be patient-centric and help patients and their physicians to make better, more-informed treatment decisions. This can be accomplished through the use of iterative solutions and high-quality pathways that are expert- and outcomes-driven, evidence-based, patient-focused, and comprehensive, and that promote research and continuous quality improvement.

Patt illustrated how clinical decision support tools bolster care delivery, explaining that the shift from volume-based to value-based care that took place under the Oncology Care Model (OCM), which was meant to improve quality and increase service value in oncology care, necessitates their use.

Before the OCM, the care delivery model consisted of a consult, financial counseling if paying out of pocket for treatment, chemotherapy education, treatment start and conclusion, and a survivorship visit, depending on diagnosis, she illustrated. However, with OCM providers required to institute 13-point care plans, the additional information required by the OCM to prove the worth of a service makes applied informatics necessary.

It is all about being more efficient and effective at the point of care, of using that information to improve care delivery.

"The OCM has been a catalyst for a lot of changes in oncology in a system that is changing dramatically. I think the only way we are going to get better is if we share information with each other, with regards to the strength and limitations of what we do. We'll get there better, faster, and safer," she concluded. ◆

BRUKINSA
IS NOW APPROVED

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with BRUKINSA monotherapy.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%) and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy.

Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

Cardiac Arrhythmias

Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Brukinsa™
zanubrutinib 80 mg capsules

BRUKINSA™ (zanubrutinib) IS A KINASE INHIBITOR INDICATED FOR THE TREATMENT OF ADULT PATIENTS WITH MANTLE CELL LYMPHOMA (MCL) WHO HAVE RECEIVED AT LEAST ONE PRIOR THERAPY.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Learn more at BRUKINSA.com

Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for at least 1 week after the last dose. Advise men to avoid fathering a child during treatment and for at least 1 week after the last dose.

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.

ADVERSE REACTIONS

The most common adverse reactions in > 10% of patients who received BRUKINSA were decreased neutrophil count (53%), decreased platelet count (39%), upper respiratory tract infection (38%), decreased white blood cell count (30%), decreased hemoglobin (29%), rash (25%), bruising (23%), diarrhea (20%), cough (20%), musculoskeletal pain (19%), pneumonia (18%), urinary tract infection (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

DRUG INTERACTIONS

CYP3A Inhibitors: When BRUKINSA is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA dose to 80 mg once daily. For coadministration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

CYP3A Inducers: Avoid coadministration with moderate or strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment: The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.

INDICATION

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Please see Brief Summary of full Prescribing Information on the following pages.

BeiGene

BRIEF SUMMARY OF PRESCRIBING INFORMATION
FOR BRUKINSA™ (zanubrutinib)
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with BRUKINSA monotherapy.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

5.2 Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

5.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%), and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy.

Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

5.4 Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

5.5 Cardiac Arrhythmias

Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

5.6 Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for at least 1 week after the last dose. Advise men to avoid fathering a child during treatment and for at least 1 week after the last dose. 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 (8.1)]*.

6 ADVERSE REACTIONS

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

- Hemorrhage *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.4)]*
- Cardiac Arrhythmias *[see Warnings and Precautions (5.5)]*

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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the WARNINGS AND PRECAUTIONS reflect exposure to BRUKINSA as a single agent at 160 mg twice daily in 524 patients in clinical trials BGB-3111-AU-003, BGB-3111-206, BGB-3111-205, BGB-3111-210, and BGB-3111-1002 and to BRUKINSA at 320 mg once daily in 105 patients in trials BGB-3111-AU-003 and BGB-3111-1002. Among 629 patients receiving BRUKINSA, 79% were exposed for 6 months or longer and 61% were exposed for greater than one year.

In this pooled safety population, the most common adverse reactions in > 10% of patients who received BRUKINSA were neutrophil count decreased (53%), platelet count decreased (39%), upper respiratory tract infection (38%), white blood cell count decreased (30%), hemoglobin decreased (29%), rash (25%), bruising (23%), diarrhea (20%), cough (20%), musculoskeletal pain (19%), pneumonia (18%), urinary tract infection (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

Mantle Cell Lymphoma (MCL)

The safety of BRUKINSA was evaluated in 118 patients with MCL who received at least one prior therapy in two single-arm clinical trials, BGB-3111-206 [NCT03206970] and BGB-3111-AU-003 [NCT02343120] *[see Clinical Studies (14.1)]*. The median age of patients who received BRUKINSA in studies BGB-3111-206 and BGB-3111-AU-003 was 62 years (range: 34 to 86), 75% were male, 75% were Asian, 21% were White, and 94% had an ECOG performance status of 0 to 1. Patients had a median of 2 prior lines of therapy (range: 1 to 4). The BGB-3111-206 trial required a platelet count ≥ 75 x 10^9/L and an absolute neutrophil count ≥ 1 x 10^9/L independent of growth factor support, hepatic enzymes ≤ 2.5 x upper limit of normal, total bilirubin ≤ 1.5 x ULN. The BGB-3111-AU-003 trial required a platelet count ≥ 50 x 10^9/L and an absolute neutrophil count ≥ 1 x 10^9/L independent of growth factor support, hepatic enzymes ≤ 3 x upper limit of normal, total bilirubin ≤ 1.5 x ULN. Both trials required a CLcr ≥ 30 mL/min. Both trials excluded patients with prior allogeneic hematopoietic stem cell transplant, exposure to a BTK inhibitor, known infection with HIV, and serologic evidence of active hepatitis B or hepatitis C infection and patients requiring strong CYP3A inhibitors or strong CYP3A inducers. Patients received BRUKINSA 160 mg twice daily or 320 mg once daily. Among patients receiving BRUKINSA, 79% were exposed for 6 months or longer and 68% were exposed for greater than one year.

Fatal events within 30 days of the last dose of BRUKINSA occurred in 8 (7%) of 118 patients with MCL. Fatal cases included pneumonia in 2 patients and cerebral hemorrhage in one patient.

Serious adverse reactions were reported in 36 patients (31%). The most frequent serious adverse reactions that occurred were pneumonia (11%) and hemorrhage (5%).

Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hepatitis B).

Table 3 summarizes the adverse reactions in BGB-3111-206 and BGB-3111-AU-003.

Table 3: Adverse Reactions (≥ 10%) in Patients Receiving BRUKINSA in BGB-3111-206 and BGB-3111-AU-003 Trials

Body System	Adverse Reaction	Percent of Patients (N=118)	
		All Grades %	Grade 3 or Higher %
Blood and lymphatic system disorders	Neutropenia and Neutrophil count decreased	38	15
	Thrombocytopenia and Platelet count decreased	27	5
	Leukopenia and White blood count decreased	25	5
	Anemia and Hemoglobin decreased	14	8
Infections and infestations	Upper respiratory tract infection¶	39	0
	Pneumonia§	15	10^
	Urinary tract infection	11	0.8
Skin and subcutaneous tissue disorders	Rashǁ	36	0
	Bruising*	14	0
Gastrointestinal disorders	Diarrhea	23	0.8
	Constipation	13	0
Vascular disorders	Hypertension	12	3.4
	Hemorrhage†	11	3.4^
Musculoskeletal and connective tissue disorders	Musculoskeletal pain‡	14	3.4
Metabolism and nutrition disorders	Hypokalemia	14	1.7
Respiratory, thoracic and mediastinal disorders	Cough	12	0

^ Includes fatal adverse reaction
* Bruising includes all related terms containing bruise, bruising, contusion, ecchymosis
† Hemorrhage includes all related terms containing hemorrhage, hematoma
‡ Musculoskeletal pain includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis
§ Pneumonia includes pneumonia, pneumonia fungal, pneumonia cryptococcal, pneumonia streptococcal, atypical pneumonia, lung infection, lower respiratory tract infection, lower respiratory tract infection bacterial, lower respiratory tract infection viral
ǁ Rash includes all related terms containing rash
¶ Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract infection viral

Other clinically significant adverse reactions that occurred in < 10% of patients with mantle cell lymphoma include major hemorrhage (defined as ≥ Grade 3 hemorrhage or CNS hemorrhage of any grade) (5%), hyperuricemia (6%) and headache (4.2%).

Table 4: Selected Laboratory Abnormalities* (> 20%) in Patients with MCL in Studies BGB-3111-206 and BGB-3111-AU-003

Laboratory Parameter	Percent of Patients (N=118)	
	All Grades (%)	Grade 3 or 4 (%)
Neutrophils decreased	45	20
Platelets decreased	40	7
Hemoglobin decreased	27	6
Lymphocytosis†	41	16
Chemistry abnormalities		
Blood uric acid increased	29	2.6
ALT increased	28	0.9
Bilirubin increased	24	0.9

* Based on laboratory measurements.
† Asymptomatic lymphocytosis is a known effect of BTK inhibition.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRUKINSA

Table 5: Drug Interactions that Affect Zanubrutinib

Moderate and Strong CYP3A Inhibitors	
Clinical Impact	• Co-administration with a moderate or strong CYP3A inhibitor increases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may increase the risk of BRUKINSA toxicities.
Prevention or management	• Reduce BRUKINSA dosage when co-administered with moderate or strong CYP3A inhibitors *[see Dosage and Administration (2.3)]*.
Moderate and Strong CYP3A Inducers	
Clinical Impact	• Co-administration with a moderate or strong CYP3A inducer decreases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may reduce BRUKINSA efficacy.
Prevention or management	• Avoid co-administration of BRUKINSA with moderate or strong CYP3A inducers *[see Dosage and Administration (2.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, BRUKINSA can cause fetal harm when administered to pregnant women. There are no available data on BRUKINSA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of zanubrutinib to pregnant rats during the period of organogenesis was associated with fetal heart malformation at approximately 5-fold human exposures *(see Data)*. Women should be advised to avoid pregnancy while taking BRUKINSA. If BRUKINSA is used during pregnancy, or if the patient becomes pregnant while taking BRUKINSA, the patient should be apprised of the potential hazard to the fetus.

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

Data

Animal Data

Embryo-fetal development toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2- or 3-chambered hearts) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose of 160 mg twice daily.

Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 150 mg/kg is approximately 32 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a pre- and post-natal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g. cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5 times the AUC in patients receiving the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of zanubrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from BRUKINSA in a breastfed child, advise lactating women not to breastfeed during treatment with BRUKINSA and for at least two weeks following the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BRUKINSA therapy.

Contraception

Females

BRUKINSA can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with BRUKINSA and for at least 1 week following the last dose of BRUKINSA. 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 BRUKINSA and for at least 1 week following the last dose of BRUKINSA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 641 patients in clinical studies with BRUKINSA, 49% were ≥ 65 years of age, while 16% were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between younger and older patients.

8.6 Renal Impairment

No dosage modification is recommended in patients with mild to moderate renal impairment (CLcr ≥ 30 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients with severe renal impairment (CLcr < 30 mL/min) or on dialysis *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment *[see Dosage and Administration (2.2)]*. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic impairment. Monitor for BRUKINSA adverse reactions in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

Distributed and Marketed by:
BeiGene USA, Inc.
San Mateo, CA 94403

Coverage by Coverage by Mary Caffrey, Gianna Melillo, Maggie L. Shaw, Jared Kaltwasser, Allison Inserro, and Matthew Gavidia

Oncology Care First Is a Big Step Toward Bundled Payments in Cancer Care, Authors Say

ONCOLOGY CARE FIRST (OCF), proposed as the successor to the Oncology Care Model (OCM), will be a major step toward shifting cancer care to bundled payments, according to leaders from an emerging network of community oncology practices.

Writing in *JCO Oncology Practice*, published by the American Society of Clinical Oncology, authors from OneOncology highlighted 3 key insights about the OCF, which could take effect by January 1, 2021. The Center for Medicare and Medicaid Innovation (CMMI) sent out a Request for Information on November 1, 2019, to replace the OCM, which involves 175 practices in a 5-year pilot to bring risk-sharing strategies to oncology care.

The OCM is built on a fee-for-service (FFS) framework, with practices receiving monthly payments to cover the cost of bringing services to patients that include better care coordination, 24/7 access to medical records, greater access to same-day appointments, and a focus on care planning and survivorship care. Most evaluations of the OCM say it has been good for patients, but that the pricing formulas lag behind the escalating costs of some innovative drugs.

While there are similarities to the OCM, the new model has features "that could have a substantial impact on practices that choose to participate," the authors write.

The OneOncology authors note the following:

- CMS wants to shift some of the FFS payment to capitation, which "will pose challenges for OCF participants." Evaluation and management (E/M) services and drug administration fees, which were previously outside the monthly practice transformation fee, would be folded inside it.
- Improved performance-based-payment formulas would do a better job of accommodating rapidly rising drug costs and protect oncologists from being held responsible for events that are beyond their control.
- New requirements may be added to require practices to gather patient-reported outcomes (PROs).

The potential challenges of gathering PROs were noted during a CMMI listening session, and the Community Oncology Alliance, an advocacy group, has called for this requirement to be phased in. Coauthor Stephen M. Schleicher, MD, MBA, discussed with *Evidence-Based Oncology*™ the apparent positive changes to the drug reimbursement formula of the OCF, which calls for making pricing adjustments by cancer type.

However, "the bundling of E/M and drug administration services into 1 prospective payment could be a sign of what may come," the authors write. They compare the proposal with what CMMI tried to do with the Radiation Oncology Model, which faced significant pushback.

Many leading OCM practices have just started the first year of 2-sided or "downside" risk, in which they face the prospect of owing Medicare money if they fail to reach predetermined financial benchmarks. With this in mind, the Community Oncology Alliance (COA), an advocacy group that has pressed for changes to the OCM, has called on CMMI to delay the start of the OCF until January 2022.

"We believe the proposed timeline is not feasible for both participating OCM practices and practices attempting to apply for OCF Model participation without prior participation in the OCM," COA said in its response to the November call for feedback. "Some practices have only just accepted a shift to down-side risk in the OCM, and most have not yet received substantial data to help them understand their performance in 2-sided risk. Forcing practices with OCM experience to immediately join 2-sided risk in the OCF Model would expose practices to significant volatility due to a range of uncertainties in the proposed payment methodology."

The authors in *JCO Oncology Practice* warn that the shift from OCM to the OCF is a greater transition than practices may realize: "These proposed changes not only represent a near-term progression toward the CMS' goal to augment its value-based payment models for cancer, they also provide signals on how CMMI may view the future of value-based care in oncology." ◆

REFERENCE

Young G, Schleicher SM, Dickson NR, Lyss AJ. Insights from the Oncology Care First proposal—where we've been and where we're going in value-based care [published online February 25, 2020]. *JCO Oncol Pract.* doi: 10.1200/JOP.20.00015.

Novel Blood Biopsy Detects MRD in Early-Stage Breast Cancer

METASTATIC DISEASE IS THE LEADING cause of death in the more than 600,000 people worldwide who die of breast cancer each year. A new blood-based assay to detect minimal residual disease (MRD) in patients with stage 0 to 3 breast cancer was shown to have 100-fold greater sensitivity compared with digital droplet polymerase chain reaction, according to results published online in *Clinical Cancer Research.*

The new test was developed by a team of Boston-based investigators, who cited the need for "more sensitive liquid biopsies, with greater dynamic range, to identify patients with MRD sooner." They noted that the new tests could also help identify higher-risk patients in some instances and avoid deleterious treatment in others.

"Our goal is to be able to turn patients who would have developed metastatic disease into patients who won't," stated co-first author Heather Parsons, MD, MPH, a medical oncologist at Dana-Farber Cancer Institute and associated scientist at the Broad Institute of Massachusetts Institute of Technology. "In the future, if we can find those patients with residual cancer early enough, determine whether they would benefit from another course of therapy, and give them an effective additional treatment, we could potentially change the course of their disease."

The investigators used retrospective analysis to identify 142 patients who underwent treatment for early-stage disease, tracking their MRD levels after curative-intent surgery at 2 main time points: postoperative (postop) (median, 3.53 months; range, 0.23-8.43) and 1 year out (median, 14.2 months; range, 6.77-21.7). The patients were followed for up to 13 years.

The patients' tumors were first analyzed via whole-exome sequencing (WES), with those results used to tailor individualized MRD tests that were run on the patients' 370 circulating cell-free DNA samples. A median of 57 mutations (range, 2-346) were targeted in each patient. Seventy-eight percent (n = 111) of patients had postop samples available, while 86% (n = 122) had 1-year samples. In addition, the median lead time between the first MRD-positive result and disease recurrence was 18.9 months (range, 3.4-39.2) in the patients with the most mutations tracked.

Distant disease recurrence was shown to be more likely if MRD was detected at the 1-year mark (HR, 20.8; 95% CI, 7.3-58.9) compared with the postop setting (HR, 5.1; 95% CI, 2.0-12.7). Also in these patients, the positive and negative predictive values came in at 0.70 and 0.77, respectively. Overall, the clinical sensitivities were 81% in patients with newly diagnosed metastatic breast cancer, 23% in the postop setting, and 19% at the 1-year mark.

"We're working to further improve the technology now to catch as many of these patients as possible," said Viktor Adalsteinsson, PhD, associate director of the Gerstner Center for Cancer Diagnostics at Broad. "When we did detect residual disease in blood, following initial courses of treatment, it was a strong predictor of future recurrence. While this was a retrospective study, if a blood biopsy can give clinicians this early warning in real time, that might provide the opportunity to alter a patient's outcome."

Despite the positive results, the authors did bring attention to 2 important study limitations. They mentioned how their blood sampling was infrequent, compared with other studies, and took place close to the same time as treatment decisions. In addition, WES was not able to identify enough mutations in every patient.

As a next step, the authors recommend that future blood-based assays aiming for extra sensitivity use whole-genome sequencing "to identify more

mutations to track in all patients." They also call for prospective studies of MRD in breast cancer that can further prove its value to the field. ◆

REFERENCE

Parsons HA, Rhoades J, Reed SC, et al. Sensitive detection of minimal residual disease in patients treated for early-stage breast cancer [published online March 13, 2020]. *Clin Can Res.* doi: 10.1158/1078-0432.CCR-19-3005.

Study Examines Fixed-Duration Therapy in Patients With MM Ineligible for Transplants

CONTINUOUS THERAPY IS LIKELY the best choice for most patients with newly diagnosed, transplant-ineligible multiple myeloma (MM), but results of a new study indicate that treatment-free intervals (TFIs) might be a good option for some patients, provided the first-line therapy is effective.

MM tends to affect the elderly. As many as 45% of new cases diagnosed in the United Kingdom are cases in which the patient is aged at least 75 years. Three in 10 patients with MM are considered frail, meaning their ability to withstand grueling treatment is limited.

At the same time, new advancements in the treatment of the incurable disease are making it possible for more people to live without the cancer progressing.

Continuous lenalidomide and dexamethasone has been shown to boost progression-free survival (PFS), as has continuous daratumumab with bortezomib, melphalan, and prednisolone. Newer research has suggested that daratumumab with lenalidomide and dexamethasone is also an effective treatment.

The combination of an elderly population with new, effective treatment options presents a conundrum for some patients and their physicians: What is the best way to maintain or boost quality of life for these patients given the incurability of the disease? In some cases, physicians and patients opt for fixed-duration therapy (FDT), with TFIs. In other cases, treatment interruptions prove necessary due to toxicities.

In a study published this month in *PLoS One*, a team of British researchers attempted to understand the results of using TFIs in MM therapy.

"In view of the recent shift towards continuous therapy, we looked to evaluate the TFI as an additional metric of efficacy in routine practice, after 1st and subsequent lines of therapy, in a large cohort of [transplant-ineligible, newly diagnosed MM] patients," wrote corresponding author Faouzi Djebbari, MPharm (Hons), MSc, of Oxford University Hospitals, in the United Kingdom.

To better understand the impact of treatment intervals, Djebbari and colleagues looked at a data set from the UK Thames Valley Cancer Network, identifying patients with transplant-ineligible, newly diagnosed MM who underwent at least 1 cycle of systemic chemotherapy between the years 2009 and 2017. Patients who had been involved in clinical trials were excluded, leaving a total of 292 subjects. The investigators wanted to evaluate the length of treatment intervals, and also compare them with overall survival (OS) rates and PFS rates.

Two-thirds of patients (67%) in the cohort responded to first-line therapy. After that round, the median TFI was 6.9 months. However, after the second round of therapy, the TFI dropped to just 1.8 months. After the third round, the TFI was just 0.6 months.

OS in the cohort was 30.2 months and median PFS was 9.0 months, although the latter varied based on the therapy chosen. The data showed that patients aged over 75 years had inferior OS and PFS rates compared with patients 75 years and younger.

Djebbari and colleagues concluded that continuous therapy is preferable to FDT for most patients, and thus providers ought to shift toward the former.

"However, when continuous therapy is not appropriate due to patient choice, or toxicities leading to discontinuation, an efficacious (not limited to thalidomide or bortezomib) but tolerable FDT strategy remains a reasonable alternative approach, which can produce a meaningful TFI," they wrote. ◆

REFERENCE

Djebbari F, Sharpley FA, McLain-Smith S, et al. Treatment-free interval as an additional measure of efficacy in a large UK dataset of transplant ineligible myeloma patients. *PLoS ONE.* 2020;15(2):e0229469. doi: 10.1371/journal.pone.0229469.

New Study Offers First Direct Comparison Between Venetoclax, Ibrutinib in CLL

VENETOCLAX HAS INCREASINGLY BECOME a prominent therapeutic option for patients with chronic lymphocytic leukemia (CLL). Now, a new study evaluates its effectiveness against another well-known therapy, ibrutinib.

Writing in the journal *Haematologica*, investigators from the United States and United Kingdom note that no such comparison has previously been made between the 2 therapies.

The study comes as treatment of the relapsing/remitting form of CLL (R/R CLL) has been dramatically reshaped by the development and approval of novel agents.

Ibrutinib is a Bruton tyrosine kinase inhibitor targeting B-cell receptor pathway signaling. First author Toby A. Eyre, MBChB, of Oxford University Hospitals in the United Kingdom, notes that the drug has shown significant benefit as a monotherapy for patients with relapsing CLL. Another drug, idelalisib, targets the same pathway and has been approved for use in combination with rituximab, an anti-CD20 agent. However, despite improvements in progression-free survival (PFS) among patients who have taken idelalisib, Eyre and colleagues say toxicity concerns have limited its use.

Venetoclax is a B-cell lymphoma–2 inhibitor, approved for use with or without rituximab.

"Venetoclax is increasingly utilized at first relapse in combination with rituximab for a 2-year fixed duration," the investigators write. "However, to date, no prospective trials have directly compared ibrutinib [with] venetoclax as [first novel agent] (NA1) in R/R CLL."

Eyre and his team sought to change that by creating a large-scale, international, multicenter study; they utilized data from previous studies evaluating each novel agent. They found data regarding 433 patients who had received ibrutinib or venetoclax as NA1, with or without an anti-CD20 agent. Of those, PFS data were available for 417 patients. Median follow-up was 14.0 months for the patients on ibrutinib (n = 385), and 13.5 months for the patients receiving venetoclax (n = 48). The primary end points of the study were overall response rate (ORR) and PFS.

The investigators found that ibrutinib was associated with a median ORR of 71% and a median PFS rate of 12%, while patients on venetoclax experienced a median ORR of 96% and a median PFS rate of 56%. Dose interruptions were reported in about one-third of patients in each cohort, and dose reductions were reported in roughly a quarter of patients for both ibrutinib (22%) and venetoclax (26%).

Discontinuation rates were 41% for ibrutinib and 25% for venetoclax. In the case of ibrutinib, the most common reasons given for discontinuation were adverse events (22%), CLL progression (8%), and Richter's transformation (2%), Tyre and colleagues write. Allogeneic stem-cell transplantation was the most common reason for discontinuation in the venetoclax cohort (10%), followed by CLL progression (4%) and unrelated death event (4%).

Venetoclax also had a superior complete response rate, which Eyre and colleagues say likely contributed to its PFS advantage over ibrutinib, but the advantage did not carry over to overall survival.

"In light of this, and in the absence of randomized data comparing these approaches, our data [provide] reassurance that either option remains a reasonable approach as NA1 in R/R CLL," the authors write.

Therefore, they conclude, the choice of an NA1 ought to be based on factors such as "individual patient factors, drug access, deliverability and patient preference." ◆

REFERENCE

Eyre TA, Lamanna N, Roeker LE, et al. Comparative analysis of targeted novel therapies in relapsed, refractory chronic lymphocytic leukaemia [published online February 20, 2020]. *Haematologica.* doi: 10.3324/haematol.2019.241539.

Fulphila®
(pegfilgrastim-jmdb) injection

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

INDICATION

Fulphila® is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Fulphila® is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

IMPORTANT SAFETY INFORMATION

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

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

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

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

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

Glomerulonephritis has been reported in patients receiving pegfilgrastim products. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after withdrawal of pegfilgrastim products. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of Fulphila®. White blood cell counts of 100 x 10^9/L or greater have been observed in patients receiving pegfilgrastim products. Monitoring of CBCs during therapy with Fulphila® is recommended.

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

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

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

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

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

FULPHILA® (pegfilgrastim-jmdb) injection, for subcutaneous use Initial U.S. Approval: 2018 Brief summary. See package insert or full prescribing information.

INDICATIONS AND USAGE
Patients with Cancer Receiving Myelosuppressive Chemotherapy

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

Limitations of Use

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS
Splenic Rupture

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

Acute Respiratory Distress Syndrome

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

Serious Allergic Reactions

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

Use in Patients with Sickle Cell Disorders

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

Glomerulonephritis

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

Leukocytosis

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

Mylan®

Capillary Leak Syndrome

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

Potential for Tumor Growth Stimulatory Effects on Malignant Cells

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

Aortitis

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

Nuclear Imaging

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

Leukocytosis

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

Immunogenicity

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

Binding antibodies to pegfilgrastim were detected using a BIAcore assay. The approximate limit of detection for this assay is 500 ng/mL.

Pre-existing binding antibodies were detected in approximately 6% (51/849) of patients with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay.

Postmarketing Experience

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

- Splenic rupture and splenomegaly (enlarged spleen) *[see Warnings and Precautions]*
- Acute respiratory distress syndrome (ARDS) *[see Warnings and Precautions]*
- Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, and urticaria, generalized erythema, and flushing *[see Warnings and Precautions]*
- Sickle cell crisis *[see Warnings and Precautions]*
- Glomerulonephritis *[see Warnings and Precautions]*
- Leukocytosis *[see Warnings and Precautions]*
- Capillary Leak Syndrome *[see Warnings and Precautions]*
- Injection site reactions
- Sweet's syndrome, (acute febrile neutrophilic dermatosis), cutaneous vasculitis
- Aortitis *[see Warnings and Precautions]*

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Although available data with Fulphila or pegfilgrastim product use in pregnant women are insufficient to establish whether there is a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes, there are available data from published studies in pregnant women exposed to filgrastim products. These studies have not established an association of filgrastim product use during pregnancy with major birth defects, miscarriage or adverse maternal or fetal outcomes.

In animal studies, no evidence of reproductive/developmental toxicity occurred in the offspring of pregnant rats that received cumulative doses of pegfilgrastim approximately 10 times the recommended human dose (based on body surface area). In pregnant rabbits, increased embryolethality and spontaneous abortions occurred at 4 times the maximum recommended human dose simultaneously with signs of maternal toxicity (see Data).

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

Data

Human Data

Retrospective studies indicate that exposure to pegfilgrastim is without significant adverse effect on fetal outcomes and neutropenia. Preterm deliveries have been reported in some patients.

Animal Data

Pregnant rabbits were dosed with pegfilgrastim subcutaneously every other day during the period of organogenesis. At cumulative doses ranging from the approximate human dose to approximately 4 times the recommended human dose (based on body surface area), the treated rabbits exhibited decreased maternal food consumption, maternal weight loss, as well as reduced fetal body weights and delayed ossification of the fetal skull; however, no structural anomalies were observed in the offspring from either study. Increased incidences of post-implantation losses and spontaneous abortions (more than half the pregnancies) were observed at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose.

Three studies were conducted in pregnant rats dosed with pegfilgrastim at cumulative doses up to approximately 10 times the recommended human dose at the following stages of gestation: during the period of organogenesis, from mating through the first half of pregnancy, and from the first trimester through delivery and lactation. No evidence of fetal loss or structural malformations was observed in any study. Cumulative doses equivalent to approximately 3 and 10 times the recommended human dose resulted in transient evidence of wavy ribs in fetuses of treated mothers (detected at the end of gestation but no longer present in pups evaluated at the end of lactation).

Lactation

Risk Summary

There are no data on the presence of pegfilgrastim in human milk, the effects on the breastfed child, or the effects on milk production. Other filgrastim products are secreted poorly into breast milk, and filgrastim products are not absorbed orally by neonates. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Fulphila and any potential adverse effects on the breastfed child from Fulphila or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of pegfilgrastim have been established in pediatric patients. No overall differences in safety were identified between adult and pediatric patients based on postmarketing surveillance and review of the scientific literature. Use of pegfilgrastim in pediatric patients for chemotherapy-induced neutropenia is based on adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients with sarcoma [see Clinical Pharmacology and Clinical Studies].

Geriatric Use

Of the 932 patients with cancer who received pegfilgrastim in clinical studies, 139 (15%) were aged 65 and over, and 18 (2%) were aged 75 and over. No overall differences in safety or effectiveness were observed between patients aged 65 and older and younger patients.

OVERDOSAGE

Overdosage of pegfilgrastim products may result in leukocytosis and bone pain. Events of edema, dyspnea, and pleural effusion have been reported in a single patient who administered pegfilgrastim on 8 consecutive days in error. In the event of overdose, the patient should be monitored for adverse reactions [see Adverse Reactions].

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenesis studies have been performed with pegfilgrastim products.

Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 6 to 9 times higher than the recommended human dose (based on body surface area).

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Advise patients of the following risks and potential risks with Fulphila:

- Splenic rupture and splenomegaly
- Acute Respiratory Distress Syndrome
- Serious allergic reactions
- Sickle cell crisis
- Glomerulonephritis
- Capillary Leak Syndrome
- Aortitis

Instruct patients who self-administer Fulphila using the single-dose prefilled syringe of the:

- Importance of following the Instructions for Use.
- Dangers of reusing syringes.
- Importance of following local requirements for proper disposal of used syringes.

Mylan®

Manufactured by:
Mylan GmbH
Steinhausen, Switzerland, CH-6312
U.S. License No. 2062

Product of India
Code No.: KR/DRUGS/KTK/28D/7/2006

Distributed by:
Mylan Institutional LLC
Rockford, IL 61103 U.S.A.

Revised: 9/2018
B:PEGFIL:R2
PEG-2019-0005

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

Produced by Gianna Melillo

NOTE: this section has been edited for clarity

Jeffrey Lowenkron, MD, MPP, Chief Medical Officer, The Villages Health

During your time at The Villages, have you observed progress in patient empowerment over care planning and more use of palliative aid to avoid unnecessary invasive treatment at the end of life?

I would say, unfortunately, no, and it's not because we don't have time. Any time you look at anything that's been evaluated over the last couple of decades related to end-of-life care, it's not the patients. The patients have already thought about it. They know what they want. They're really hoping somebody would ask them. We never ask them. In primary care, I don't know the numbers now, [but] it used to be about 4% of the time we asked them, even though 80% of the time they thought about what they wanted and knew. I would say the only group that's probably worse at doing advanced directives and palliative care than primary care is oncology. For the folks that have oncology problems, the likelihood that they'll get palliative care at the right time or even hospice at the right time, I would say it's unfortunately delayed.

Is the expansion of Medicare Advantage a plus or a minus for oncology care in your view?

I think the expansion of Medicare Advantage, it's always a plus for the patient. Because what Medicare Advantage does, as opposed to the fee-for-service world, is it links and aligns patient outcomes with care delivery. As patients do better, the care delivery systems do better, and as patients do worse, the care delivery systems do worse. In the typical fee-for-service model, generally the care delivery system can do really, really well, and the patients may do very, very poorly. They don't have to align. From the perspective of the patients, it's always a better care model and payment model to be in Medicare Advantage than traditional fee-for-service.

From the oncology perspective specifically, there are going to be some challenges because obviously with the expansiveness of very expensive medications in the oncology world, the difficulty of figuring out how to pay for those is a real challenge. I can't tell you whether it's going to be better or worse for them over time. ◆

Maen Hussein, MD, Physician Director of Finance, Florida Cancer Specialists

What will CMS's proposed change in the way Medicare Advantage pays for hospice mean for community oncology practices?

I think that hospice is being underutilized in caring for our patients. There is this mentality that hospice means that the patient is going to die very soon. That's really not true. There are more data showing that palliative care and hospice actually help improve the quality of life, and in some cases, even survivorship. I believe that the new changes will help and encourage the oncologists to bring up that topic sooner than later, and maybe help the patient accept that concept, and change the culture to understand that being under hospice care doesn't mean you're dying tomorrow. The indication for hospice, if the patient has survived, it's less than 6 months, and that actually can be extended. It doesn't mean that you're even dying within 6 months, but that's usually the period and if the patient lived to 6 months, you can even extend that. That will encourage the physicians to approach the patient sooner than later; talking about the option of hospice. I can see that culture change. I've been practicing here for almost 15 years now. It was much harder to talk about hospice before than now, especially when you explain to the patient that this is not the end, you're not giving up. But it's a way to focus on your pain and discomfort and still allow for some palliative therapies. A lot of hospice now are [willing] to pay for radiation therapy as palliative [care], or even sometimes some forms of chemotherapy.

The Oncology Care Model (OCM) has been criticized for failing to adequately account for high-cost drugs for some patients. Have you seen improvements in the proposed Oncology Care First model and which proposed change do you believe is the most important?

I think it's still early to judge if the changes [will] have an impact. I think one of the things that seemed to be promising is that they have the risk assessment for each cancer, so they have the risk stratification. That might help in the future to assess for each type of cancer, how much it will cost to treat those patients. That will help in the bundled payment in the future. ◆

Rebecca Kirch, JD, executive vice president, Health Care, Quality and Value, National Patient Advocate Foundation

What obstacles continue to prove an issue within oncology? What further research is warranted to address these issues?

There are some interesting challenges in the form of language barriers, and old habits that die hard. [At the meeting of the Association of Community Cancer Centers,] we talked about the importance of integrating palliative care, and the first question was, "Well, who provides that?" Depending on when you were trained in your practice, you might have learned palliative care as something different from what it is today and what the evidence shows. So today, what palliative care is, is an essential aspect of good quality cancer care from diagnosis onward to optimize quality-of-life.

Whose job is it? It's everybody's job. Every clinical encounter needs to include some aspects of helping with care coordination, identifying what's bothering the patient and caregiver most, because they're an essential unit of care. The opportunity we have to use the skilled communication that is sort of at the core palliative care principle for all frontline clinicians to be equipped and confident and engaged in doing, I think will make a significant difference for how value-based care unfolds, how payment reform happens, how the lived experience plays out for patients and families to be a better one, irrespective of the prognosis of the trajectory.

If we emphasize the importance of those skills, and the opportunities to address financial impairments and functional impairments through navigation

to these services that people need that focus on what they say matters to them, then we're delivering truly person-centered care and the promise of what that can be. If we keep emphasizing disease-directed treatment without thinking about quality-of-life, and the person beyond the disease, we're going to fall short of all of those goals that we all hold dear. ◆

Michael Diaz, MD, President of Community Oncology Alliance and Assistant Managing Physician at Florida Cancer Specialists

In its response to the Oncology Care First request for feedback, COA recommended a delay in the start of the successor model to January 1, 2022. How will having more time in the OCM benefit practices?

Well, there are several reasons. First of all, 2021 is less than a year away, and we don't have details on this new model. In order to have practices evolve, change, and implement new processes — and I think that's one of the key things here — there are a lot of new fundamental components that are different than the Oncology Care Model (OCM). We want to make sure that practices have adequate time to learn, understand, adapt, and modify. We're wanting to extend the Oncology Care Model in essence, to actually delay the initiation of the Oncology [Care] First model. That's the most important thing.

Some people will say, "Well, why can't you just complete the Oncology Care Model, delay the Oncology Care First model 6 months to a year?" Well, all the practices already had this infrastructure set up for this type of system process. We have care coordinators, we have layers and layers of new systems that we've developed to be able to participate in these value-based care models, these alternative payment models. Without participating in a model, you can't keep and maintain your fundamental infrastructure. The majority of the practices, we feel, would experience some financial hardships trying to maintain those components of their practice if they're not participating in them all. We just think that it would help ease a transition.

Another more significant reason has to do with the fact that the Oncology Care First model, when you start in it, right now, the way it's designed, you start off in a 2-sided risk. We would like for as many community oncology practices to be able to participate in this, and not all are participating in the 2-sided risk of the Oncology Care Model. We just think a delay would allow more time to allow more practices to evolve to be able to participate.

Are you receiving any early feedback from practices that have moved to 2-sided risk?

We have been hearing from other practices. I think that because right now we're still getting feedback from the later performance periods, before people had to switch in 2-sided risk, we're getting mixed results, because not everybody is in 2-sided risk in the first place. Those that have gone to 2-sided risk, some are doing extremely well. I have not heard from those that are in 2-sided risk and have not done well. The only other things that I have heard is that as we proceed, and we get data from subsequent pay periods, things are changing and people aren't performing as well as they thought they might. They're not sure why but there's just a delay in the time required for the feedback. I haven't heard anything from the practices since we had to decide to accept the 2-sided risk model for this period, but I'm sure that we will hear more as time evolves. That's another reason why it wouldn't necessarily be a bad idea to sort of delay the initiation of a new model, because the amount of time in between the period during which we're taking care of patients and the time we get the feedback, there's such a delay. It's a little difficult to make changes very quickly, because we just don't get the information very quickly. We just need the time to improve our processes. If we could narrow down the time interval from when we are seeing patients in the performance period to the time we get the information results and understand why we did how we did, if we can get that time interval narrowed down, then it would probably be easier to transition and evolve at a faster rate.

What are the most important lessons from the OCM that Florida Cancer Specialists can share with other community practices that are moving to alternative payment models?

I thought about this because we've been working at this very diligently for the past several years. I would say, it takes a lot of collaboration. You need to network with the other practices involved. You need to share ideas. You need to network with specialists that understand the data that you're receiving from CMS. Because whenever you get the data, it's not very easy to interpret or understand, so you need to work with a specialist that can help sift through all the details so that you can understand why your practice performed the way that you did. Until you know that information, it's very difficult, very difficult to make improvements. Networking, working with experts, I would say those are the main things. Also, you have to get the physicians involved and you have to get their buy in. They have to really understand the importance and believe in it and understand why they're doing it. I think that if you get all those major components aligned, along with having very good management, practice management that can sort of glue all that together, I think that helps to optimize success in any form of alternative payment model including Oncology Care Model. ◆

Lucio Gordan, MD, President & Managing Physician, Florida Cancer Specialists

In your opinion, does the proposed Oncology Care First model go far enough to address concerns that the OCM did not adequately reimburse practices for high-cost therapies? Why or why not?

The Oncology Care First model remains very difficult to understand, in my opinion. I think Community Oncology Alliance and others have sent several initial suggestions and recommendations to CMS, CMMI (Center for Medicare and Medicaid Innovation) as to how to design Oncology Care First. I am not convinced yet that Oncology Care First truly takes into account the necessary elements, including high-cost drugs. I think we lack understanding as far as the details, as to how this will be operationalized. We really have embraced the Oncology Care Model. We do think that value-based care should obviously continue in cancer care in the United States. It is just taking maybe too quick of a step from moving from the current Oncology Care Model to Oncology Care First. There are a lot of things that need to be understood and the details need to be ironed out for us to truly embrace this as a solution for us.

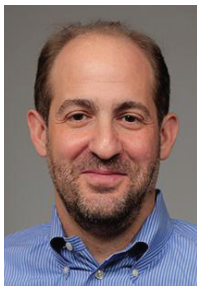
Have you seen any shifts that suggest payers are recognizing cost differentials between hospital and community oncology settings in cancer care?

I have seen a significant improvement in understanding of the site of care issues as far as cost, as we compare hospital systems versus community oncology. I haven't seen enough action and results yet. Clearly, the payers do understand the dynamics and the importance of fixing the issue. Hopefully we'll get there. The steps have been small and moving slowly, but I'm relatively optimistic that we'll get there, hopefully in the near future, as far as improved transition from site of care from hospital-based to community-based systems. ◆

COA to Present Virtual Conference Due to COVID-19
Read more at: ajmc.com/link/4568

The Need for a Serious Illness Digital Ecosystem (SIDE) to Improve Outcomes for Patients Receiving Palliative and Hospice Care

Jonathan Nicolla, MBA; Hayden B. Bosworth, PhD; Sharron L. Docherty, PhD, PNP-BC; Kathryn I. Pollak, PhD; Jeremy Powell, MEd; Nichole Sellers, BA; Bryce B. Reeve, PhD; Greg Samsa, PhD; Linda Sutton, MD; and Arif Kamal, MD, MBA, MHS



BOSWORTH

Hayden B. Bosworth, PhD, Department of Population Health Sciences, Duke University School of Medicine

NICOLLA

Jonathan Nicolla, MBA, Duke Cancer Institute

POLLAK

Kathryn I. Pollak, PhD; Professor in Population Health Sciences, Duke University School of Medicine

DOCHERTY

Sharron L. Docherty, PhD, PNP-BC, Duke School of Nursing

SELLERS

Nichole Sellers, BA, Acclivity Health Solutions

POWELL

Jeremy Powell, MEd, Acclivity Health Solutions

Abstract

Palliative and hospice care services produce immense benefits for patients living with serious illness and for their families. Due to the national shift toward value-based payment models, health systems and payers share a heightened awareness of the need to incorporate palliative and hospice services into their service mix for seriously ill patient populations.

During the last decade, a tremendous amount of capital has been invested to better integrate information technology into healthcare. This includes development of technologies to promote utilization of palliative and hospice services. However, no coordinated strategy exists to link such efforts together to create a cohesive strategy that transitions from identification of patients through receipt of services.

A Serious Illness Digital Ecosystem (SIDE) is the intentional aggregation of disparate digital and mobile health technologies into a single system that connects all of the actors involved in serious illness patient care. A SIDE leverages deployed health technologies across disease continuums and geographic locations of care to facilitate the flow of information among patients, providers, health systems, and payers. Five pillars constitute a SIDE, and each one is critical to the success of the system. The 5 pillars of a SIDE are: Identification, Education, Engagement, Service Delivery, and Remote Monitoring.

As information technology continues to evolve and becomes a part of the care delivery landscape, it is necessary to develop cohesive ecosystems that inform all parts of the serious illness patient experience and identifies patients for the right services, at the right time. ◆

CONTINUED FROM COVER

Due to the national shift toward value-based payment models, health systems and payers share a heightened motivation to incorporate palliative and hospice services into their service mix for seriously ill patient populations. For instance, health systems currently leverage palliative care specialists to complement other specialists (eg, pulmonologists, oncologists) as an extension of the care team to "provide an extra layer of support." Palliative care specialists also provide oversight and accountability for patients' issues ancillary to disease-directed treatments.[2] In addition, health systems have integrated community hospice staff into serious illness delivery settings to socialize hospice care benefits with patients early in their disease progressions.[3] However, despite an increased emphasis on these services, many patients who could benefit from palliative and hospice care do not access the care.[4-6]

During the last decade, a tremendous amount of capital has been invested to better integrate information technology into healthcare.[7] These investments include development of technologies to promote utilization or completion of palliative care services and activities. But the entrance of specialized solutions into the marketplace has created a fragmented mobile health landscape, as many solutions have been designed to solve narrow problems.[8,9] For instance, health systems have invested in technologies that specialize in identifying patients with serious illness that, because of increased risk of poor outcomes (eg, hospitalization, death), may benefit from care by specialty palliative care services. Similarly, health systems have invested in technologies that guide patients through completing advance care planning documentation. Although these solutions may solve discrete problems, no coordinated and comprehensive strategy exists to link such efforts together to create a cohesive approach that seamlessly transitions from identification of patients through receipt of palliative and hospice care services.

The Serious Illness Digital Ecosystem

The Serious Illness Digital Ecosystem (SIDE) is the intentional aggregation of disparate digital and mobile health technologies into a single system that connects all of the actors involved in serious illness patient care. A SIDE leverages deployed health technologies across disease continuums and geographic locations of care to facilitate the flow of information among patients, providers, health systems, and payers. A SIDE represents a holistic approach to serious illness patient and population management that eliminates barriers created by niche solutions, establishing a heightened level of connectivity between the patient and all other key stakeholders.

A SIDE recognizes the need of each component of the ecosystem to thrive, allowing the system to provide better insights into the patients it serves. Cyclical in nature, no single component of the ecosystem is more valuable than the next and cannot be optimized without the last. Five pillars constitute a SIDE and each one is critical to the success of the system. The 5 pillars of a SIDE are: Identification, Education, Engagement, Service Delivery, and Remote Monitoring.

Each pillar of a SIDE allows a health system to answer a specific fundamental question about their serious illness patent population. In such a population, the typical entry point for a patient into a SIDE is through the Identification pillar. This is where a health system, payer, or other accountable entity can answer the question, "How do we identify the right patients for palliative and hospice services?"

In the Education pillar, stakeholders can answer the question, "Now that we have identified patients who qualify for these services, how can we educate them on the benefits of these services?" While education is important, research shows that merely educating a patient on these services, if not accompanied by patient engagement, is ineffective in converting a patient into a user of palliative and hospice care services.[10,11]

From the Education pillar, a patient transitions to the Engagement pillar, which answers the question, "Once we have educated the patient on the benefits of these services, how do we empower them to participate in palliative care or share their care preferences with their clinical team?"

As a patient and their caregiver(s) become further engaged in the patient's care, we transition to the fourth pillar, Service Delivery, which answers the question, "How can we provide usable information to the clinical team to impact delivery of care?" This includes pre-visit assessments of unmet needs, priorities for care, and goals and preferences for the interactions with the palliative care team.

Finally, once an informed treatment plan is in place and a clinical encounter is completed, the patient moves to the fifth pillar, Remote Monitoring, where the SIDE answers the question, "How do we determine the health of a patient away from a clinical visit to ensure their continued well-being?"

As a patient transitions through all 5 pillars of the SIDE, patient, caregiver, and administrative data are being collected. These data are integrated back into the SIDE model to further inform the Identification pillar, allowing the system to continually learn from itself and better manage future seriously ill patients who enter the ecosystem.

Identification

Despite administrative measures to improve usage of hospice and palliative care services, it is often difficult for health systems to determine patient suitability and to time delivery of these services. Daunting challenges presented by prognostication difficulties and rapidly evolving treatment paradigms require that information beyond clinician intuition and estimation be used. Utilizing "big data" is a potentially efficient way to synthesize medical information for a given patient and contrast it against data about similar patients within a population to accurately identify which patients would most benefit from palliative and hospice services.

Health systems that utilize predictive analytics, advanced algorithms, machine learning, and artificial intelligence are able to manage large patient populations. Rather than relying merely on clinical intuition and experiential prognostication, these tools often allow health systems to more quickly and accurately identify patients who are appropriate for these services by combining available data from administrative, billing, and clinical data sets. Coupling this analytic ability with clinical intuition allows health systems to initiate the process of enrolling the right patients into the right services at the right time, leading to improved patient outcomes and cost savings for the health system.

Systems in the marketplace have demonstrated that using a machine learning or artificial intelligence solution can increase efficiency, lower cost, and improve patient experience. Most notably, Stanford University established in 2017 that using a deep neural network and historic electronic health record information to mark patients who would benefit from palliative care could return prognostication at 3, 6, 9, and 12 months on a patient's likelihood to die. Commercialization of such models provide clinicians with a prepopulated list that can be more than 90% accurate in predicting death in the next 3, 6, 9, or 12 months.[12]

Education

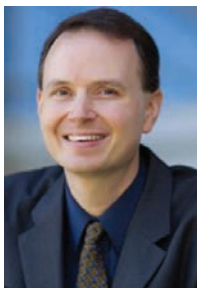
As patients are identified within a health system for palliative or hospice services, the next challenge becomes connecting them to these services. A key driver of the underutilization of palliative and hospice care services is a patient's knowledge gap: having misconceptions about the benefits of these services, including hospice care and palliative care, and about how these services can be integrated into the usual care experience. In one recent large survey, 71% of patients could not accurately articulate the difference between hospice and palliative care, often confusing the care goals of the 2 services.[13] For this reason, and possibly others, patients eligible for palliative care hesitate to enroll despite its benefits. This knowledge barrier carries similar implications for patients who may be eligible to receive hospice benefits.

Some of the most widespread use of digital engagement platforms in the serious illness space has been within advanced care planning. Traditionally, health systems have had difficulty in messaging and operationalizing advance care planning, often leading to inaction and confusion among patients, providers, and family members.

To close the gap between patients who are identified for hospice and palliative services and the utilization of these resources, the Education pillar of the SIDE model emphasizes the need for patients to access targeted, understandable, just-in-time content. In multiple instances, digital health platforms have been successfully deployed to educate patients on the benefits of hospice and palliative care. For instance, PCforMe, a web-based mobile health platform, uses short videos to educate seriously ill patients on the benefits of palliative care, covering topics such as "What is palliative care?" and "How is palliative care different than hospice care?"[12] Additionally, ACP Decisions has created and tested series of educational videos that prepare patients and family members to have discussions with their medical team about serious illness and planning for the future, and offer ways to incorporate these conversations into their treatment plans.[14]

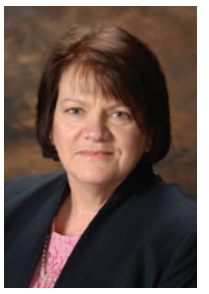
Engagement

Education is an important first step in activating a patient; next, health systems must engage the patient in care planning with their clinicians. Historically, health systems have faced challenges in promoting active participation by patients and family members in planning their care.[15] Utilizing digital tools in the SIDE model allows a health system to achieve the following with patients: (1) Contextualization: Patients need a space to contextualize the care services they need to their individual preferences; (2) Application: Patients need tools that will allow them to organize their thoughts into an action plan that can be shared with their clinical team; and (3) Empowerment: Patients need a mechanism to help them convey their preferences to their care team and to facilitate »



REEVE
Bryce B. Reeve, PhD, Duke Department of Population Health Management

SAMSA
Greg Samsa, PhD, Department of Population Health Sciences, Duke University School of Medicine



SUTTON
Linda Sutton, MD, Duke Cancer Network

KAMAL
Arif H Kamal MD, MBA, MHS; Associate Professor of Medicine, Business Administration, and Population Health Sciences, Duke Cancer Institute, Duke Fuqua School of Business

conversations that lead to actionable changes, ones that incorporate the patient's preferences for their treatment plan.

To date, some of the most widespread use of digital engagement platforms in the serious illness space has been within advance care planning. Traditionally, health systems have had difficulty in messaging and operationalizing advance care planning, often leading to inaction and confusion among patients, providers, and family members during the most critical moments of patient care.[16] In response, patient engagement websites have been designed that use simple technology and social media to help patients create and share their advance care planning wishes with their clinicians. Further, technology companies have partnered with health systems to establish a simple patient engagement solution that facilitates the advance care planning documentation process for the patient and provides a universal repository system for advance care planning documentation.

Service Delivery

After a health system has identified, educated, and engaged patients and their families, how is this translated into service delivery for the patient? Patients seek a more active role in sharing their preferences and in guiding clinical care that addresses their concerns, priorities, and preferences.[17] The SIDE model recognizes that the information a patient provides is only as effective as the ability of the care team to execute their wishes. Clinicians need to collect information from patients in a way that allows them to easily locate, understand, and apply patient preference into their care plan.

Effective outputs from patient engagement tools must accomplish 3 goals for the clinician:

1. Clinicians must be able to easily access and navigate the preferences of a patient.
2. The information from the patient must be presented in such a way that it can be easily understood by the clinician.
3. The information must facilitate a conversation between the clinician and patient about how to incorporate patient preference into the care plan.

Successful patient engagement tools focus not only on capturing the patient voice, but also the ability to impact service delivery for clinicians.[18] For example, Cake, a web-based end-of-life planning tool developed by the Massachusetts Coalition for Serious Illness Care, first asks a patient to complete a series of questionnaires regarding end-of-life preferences. Then, the tool packages the patient's responses into a PDF packet that can be easily shared with the clinician, allowing the clinician to better understand how to incorporate the patient's preferences into care planning.

Remote Monitoring

Overwhelmingly, the majority of the patient experience with serious illness happens outside a clinical setting. Patient distress, symptom burden, and functional limitations are experienced away from healthcare professionals, often in their own homes alongside loved ones and informal caregivers. However, health systems have very little actionable insight for what is happening to patients while they continue their daily routine. Often, during the weeks or months between clinical appointments, the well-being of patients with serious illness can drastically change. Therefore, at the time of a consultation with the patient, clinicians are obtaining a snapshot of information at that point in time, rather than longitudinal information around the time when the patient experienced the challenges. This can lead to a loss of valuable time for a patient and clinician, causing a lag in care that can impact numerous outcomes for the patient. For this reason, the final vital component of a SIDE is remote patient monitoring, which provides clinical insight into the well-being of patients to the clinical team in real time.

Traditional patient home-based monitoring has been primarily conducted by clinical staff using a telephone to perform checkups on patients or to reconnect with patients who call a triage line with a question or concern. While this technique can be helpful for patients and caregivers to obtain information, it presents limitations regarding how that information can be used to improve patient care. First, by nature, phone calls allow only for the capture of unstructured data, leading to variation in the capture and interpretation of the data. Second, because the data-capture method occurs outside of a technology platform, it is difficult to utilize these data to inform urgency of care or perform a needs assessment across a population. Lastly, as these data are not presented in a structured way into an analytics engine, the ability to learn based off its existing population and improve on its ability to identify patients is greatly limited. By structuring this process in a SIDE, we allow the system to accomplish the following: to (1) improve identification of patients; (2) integrate routine collection of data on distress, symptom burden, and functional impact using validated questionnaires that are shared with the clinical team; (3) allow patients to feel more connected to their clinical team as they are providing constant feedback away from the clinic; and (4) efficiently utilize clinical staffing resources.

Conclusions

As information technology continues to evolve and become a part of the care delivery landscape, it is necessary to develop cohesive medical ecosystems that inform all parts of the patient experience and align patients in the right services, at the right time. This is particularly important for patients suffering from serious illness. Application of a SIDE provides numerous benefits for patients, family caregivers, and health systems by optimizing appropriateness and timeliness of care, leading to an increase in utilization of palliative and hospice care services. ◆

ACKNOWLEDGMENTS

The authors would like to acknowledge Duane Feger for his contributions in framing the Identification section of the manuscript and Anne Perez for her contributions in the design of the accompanying graphic of the manuscript.

DISCLOSURES

JN is an owner and president of Prepped Health, LLC, and chief product officer of Acclivity Health Solutions Inc. JP is founder and chief executive officer of Acclivity Health Solutions Inc. NS is employed by Acclivity Health Solutions Inc. AK is an owner and chief executive officer of Prepped Health, LLC, and chief medical officer of Acclivity Health Solutions Inc.

ADDITIONAL AUTHOR INFORMATION

Duke Cancer Institute (JN), Durham, NC; Department of Population Health Sciences, Duke University School of Medicine (HBB, KIP, GS), Durham, NC; Duke School of Nursing (SLD), Durham, NC; Acclivity Health Solutions (JP and NS); Center for Health Measurement, Duke Department of Population Health Management (BBR), Durham, NC; Duke Cancer Network (LS), Durham, NC; Duke Cancer Institute and Duke University Fuqua School of Business (AK), Durham, NC.

REFERENCES

1. McAteer R, Wellbery C. Palliative care: benefits, barriers, and best practices. *Am Fam Physician*. 2013;88(12):807-813.
2. Smith TJ, Coyne P, Cassel B, Penberthy L, Hopson A, Hager MA. A high-volume specialist palliative care unit and team may reduce in-hospital end-of-life care costs. *J Palliat Med*. 2003;6(5):699-705. doi: 10.1089/109662103322515202.
3. Farber S. Hospice volunteer training for health science students: an academic medical center-hospice community partnership. *J Palliat Med*. 2001;4(1):60-64. doi: 10.1089/109662101300052022.
4. Kathpalia P, Smith A, Lai JC. Underutilization of palliative care services in the liver transplant population. *World J Transplant* 2016;6(3):594-598. doi: 10.5500/wjt.v6.i3.594.
5. Hayward B, Zappetti D. Palliative care for patients with advanced chronic obstructive pulmonary disease (COPD) remains underutilized. *Clin Pulm Med*. 2019;26(3):102. doi: 10.1097/CPM.0000000000000309.
6. Fine PG. Hospice underutilization in the U.S.: the misalignment of regulatory policy and clinical reality. *J Pain Symptom Manage*. 2018;56(5):808-815. doi: 10.1016/j.jpainsymman.2018.08.005.
7. Gondi S, Song Z. The burgeoning role of venture capital in health care. *Health Affairs* website. healthaffairs.org/do/10.1377/hblog20181218.956406/full/ Published January 2, 2019. Accessed February 11, 2020.
8. Woolf SH, Johnson RE. The break-even point: when medical advances are less important than improving the fidelity with which they are delivered. *Ann Fam Med*. 2005;3(5):545-552. doi: 10.1370/afm.406.
9. Stange KC. The problem of fragmentation and the need for integrative solutions. *Ann Fam Med*. 2009;7(2):100-103. doi: 10.1370/afm.971.
10. Jaarsma T, Abu-Saad HH, Dracup K, Halfens R. Self-care behaviour of patients with heart failure. *Scand J Caring Sci*. 2013;14(2):112-119. doi: 10.1111/j.1471-6712.2000.tb00571.x.
11. Coulter A. *Engaging Patients in Healthcare*. Maidenhead, Berkshire, UK: Open University Press; 2011.
12. Avati A, Jung K, Harman S, Downing L, Ng A, Shah NH. Improving palliative care with deep learning. *BMC Med Inform Decis Mak*. 2018;18(Suppl 4):122. doi: 10.1186/s12911-018-0677-8.
13. Huo J, Hong YR, Grewal R, et al. Knowledge of palliative care among American adults: 2018 Health Information National Trends survey. *J Pain Symptom Manage*. 2019;58(1):39-47.e3. doi: 10.1016/j.jpainsymman.2019.03.014.
14. Kamal A, Friedman F, Nicolla J, Davis DM. Evaluation of a mobile application to prepare and engage cancer patients prior to a palliative care (PC) visit: results of a randomized, controlled trial. *J Clin Oncol*. 2018;36(15 suppl):abstr 10103. doi: 10.1200/JCO.2018.36.15_suppl.10103.
15. Volandes AE, Paasche-Orlow MK, Barry MJ, et al. Video decision support tool for advance care planning in dementia: randomised controlled trial. *BMJ*. 2009;338:b2159. doi: 10.1136/bmj.b2159.
16. Seale H, Travaglia J, Chughtai AA, Phillipson L, Novytska Y, Kaur R. 'I don't want to cause any trouble': the attitudes of hospital patients towards patient empowerment strategies to reduce healthcare-acquired infections. *J Infec Prev*. 2015;16(4):167-173. doi: 10.1177/1757177415588378.
17. Sharp T, Moran E, Kuhn I, Barclay S. Do the elderly have a voice? advance care planning discussions with frail and older individuals: a systematic literature review and narrative synthesis. *Br J Gen Pract*. 2013;63(615):e657-e668. doi: 10.3399/bjgp13X673667.
18. Say R, Murtagh M, Thomson R. Patients' preference for involvement in medical decision making: a narrative review. *Patient Educ Couns*. 2006;60(2):102-114. doi: 10.1016/j.pec.2005.02.003.

Why Palliative Care Is the Answer to the Serious Illness Question in Payment Reform

Maggie R. Salinger MD, MPP; Nathan A. Boucher, DrPH, PA, MS, MPA; Thomas W. LeBlanc, MD, MA; Kevin C. Oeffinger, MD; Kathryn I. Pollak, PhD; Jesse D. Troy, PhD; and Arif H. Kamal MD, MBA, MHS

CONTINUED FROM COVER

APMs establish budget targets on the basis of either patient populations or care episodes, which creates an incentive for provider networks to cut total spending. APMs also use an array of quality metrics related to: (1) optimizing patient outcomes (eg, rates of hospitalization and mortality or attainment of disease-specific treatment goals), (2) improving health service delivery (eg, accessibility of services or adherence to gold standard therapies), and (3) increasing patient-centeredness (eg, utilization of advance directives or measures of patient satisfaction).[1]

The changing financial frontier has pushed our medical system to expand its reach to achieve healthcare's Triple Aim as proposed by the Institute for Healthcare Improvement.[2] For provider networks, this translates to offering better and broader services but at a lower cost, an objective that is especially challenging when managing seriously ill patients. Seriously ill patients have an elevated risk of mortality, impairments in functional status, and/or medical conditions with burdensome symptoms. This patient population is growing in number and accounts for a vastly disproportionate amount of healthcare spending.[3]

Health administrators and clinicians alike recognize that meeting the extensive medical and social needs of the seriously ill may no longer be the revenue boon it once was in the fee-for-service era. The transition to pay-for-performance, and especially the inclusion of downsided risk in APM reimbursement schemes, means practices will now face serious threats to long-term sustainability if they cannot meet quality metrics.

In response to the constellation of APM incentives, provider networks have strengthened their capacity to systematically identify and monitor their sickest cohorts. Some have even begun to predict adverse outcomes at the individual level, knowing in advance that a patient may be at high risk for hospitalization or death.[4] However, even with the technological advances in the use of big data and predictive modeling, there is still uncertainty about how to best respond. In a survey of a large, representative sample of accountable care organizations (ACOs), Bleser et al discovered that 94% employ measures to define their seriously ill populations, but that only 8% to 21% of ACOs have either "partially" or "widely" implemented clinical programs targeting these groups.[5]

At this stage of system-wide reform, the question is not *whether* provider networks should augment our medical and social infrastructure for the seriously ill, but *how*. Looking ahead, it is clear that building the ideal future will require greater integration of palliative care principles. Insights from specialty palliative care would enable systems to better manage those patients who place the greatest demands on the system. Palliative care has a growing body of evidence demonstrating its contribution to our industry's Triple Aim by lowering 30-day readmission rates, by reducing the total costs of care at end of life, and by increasing patient well-being and satisfaction.[6-12]

More than a specialty, palliative care represents a philosophical approach to treatment that focuses on reducing suffering and increasing quality of life. Palliative care delivery comes in 3 levels: primary, champion, and specialty.[13] Primary palliative care is the common, fundamental palliative care delivered by every clinician to every patient with serious illness. It comprises basic symptom management and goal setting by which primary and specialty clinicians (eg, cardiologists, oncologists) are experienced and comfortable. Champion palliative care is provided by clinicians with additional training who serve as advocates for expanded palliative care services in their hospital units, clinics, and other local settings. Specialty palliative care is supported by clinicians who have undergone formal fellowship or other training that establishes an advanced expertise in the field.

A common misconception about specialty palliative care is that it is beneficial only when integrated into the care of the terminally ill. Although there is indeed a subset of palliative care that assists patients and families in the immediate phases before death, the scope of this discipline extends far beyond end-of-life care, such as hospice care. Afterall, a therapeutic emphasis on patient comfort and family support is relevant at all phases of disease, including as early as diagnosis.

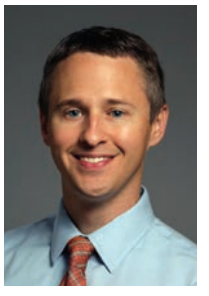
For seriously ill populations, all medical encounters from the time of diagnoses onward should be regarded as potential opportunities to intervene in a palliative manner. The incentive to do so at earlier stages and in broader contexts is especially compelling when managing cohorts whose diseases have well-characterized patterns of progression.

Palliative care's patient-centered approach tends to incorporate skillsets of multiple clinicians, such as physicians, advanced practitioners (eg, nurse practitioners, physician assistants), nurses, social workers, physical and occupational therapists, and chaplains. These team members offer care in a variety of settings, like hospitals, community clinics, or homes. The types of services encapsulated in a palliative approach are aimed at educating patients and families about disease trajectories, minimizing symptom burden, leading goals of care discussions, addressing conflict and mistrust, identifying surrogate decision makers, connecting families to community resources, and linking patients with home-based support. When delivered in a nonhospice context, these palliative measures take place alongside disease-targeted therapies, such as hemodialysis for advanced kidney disease, chemotherapy for cancer, or inotropes for heart failure.

For seriously ill populations, all medical encounters from the time of diagnoses onward should be regarded as potential opportunities to intervene in a palliative manner. The incentive to do so at earlier stages and in broader contexts is especially compelling when managing cohorts whose diseases have well-characterized patterns of progression. Examples include heart failure, lung disease, kidney disease, dementia, and advanced cancers, each of which has a pattern whereby hospital admissions may be harbingers for further or more rapid decline. As such, these hospital admissions also tend to mark the beginnings of "new baselines," »

SALINGER
Maggie R. Salinger, MD, MPP; Resident Physician at Duke University Hospital

BOUCHER
Nathan A. Boucher, DrPH, PA, MS, MPA; Assistant Research Professor in the Sanford School of Public Policy, Duke University

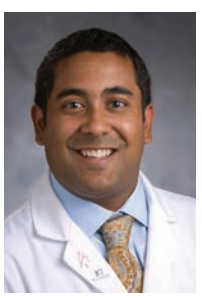


LEBLANC
Thomas W. LeBlanc, MD, MA; Associate Professor of Medicine, Duke University School of Medicine

OEFFINGER
Kevin C. Oeffinger, MD; Professor of Medicine, Duke University School of Medicine

POLLAK
Kathryn I. Pollak, PhD; Professor in Population Health Sciences, Duke University School of Medicine

TROY
Jesse D. Troy, PhD; Assistant Professor of Pediatrics, Duke University School of Medicine



KAMAL
Arif H. Kamal MD, MBA, MHS; Associate Professor of Medicine, Business Administration, and Population Health Sciences, Duke Cancer Institute, Duke Fuqua School of Business

since it is uncommon for seriously ill patients to return to the level of functioning they had prior to hospitalization.

The value of early palliative methods has been demonstrated by multiple APM-inspired outreach programs targeting seriously ill cohorts. For example, Vidant Health is an ACO serving a rural population that is socioeconomically disadvantaged. Catering to their sickest patients, Vidant Health has launched technology-assisted home monitoring systems, care alignment strategies, and community partnerships, typically with faith-based organizations. Together, these initiatives have generated shared savings through Medicare and have led to lower readmission rates, which declined from 10% to 20% to 1.5% to 5%).[5] Another exemplar ACO, Facey Medical Group has designed a community-based program that includes a 24/7 call center, a palliative-trained physician, nurse practitioners, care managers, social workers, and chaplain services. They reported high levels of patient satisfaction, 68% fewer hospitalizations, and 55% fewer emergency department visits.[5]

When seriously ill patients do experience a hospitalization, they are at greater risk of requiring intensive care. Evaluations of structured palliative programming in this setting help to demonstrate the profound impact of aligning care goals, an impact that could extend to other contexts of care as well. Kyeremanteng et al's systematic review of formal palliative care consultations in intensive care units (ICUs) showed a reduction in ICU length of stay (LOS) compared with those who did not receive the consultations.[14] A separate systematic review and meta-analysis by Bibas et al examined a specific palliative intervention designating surrogate decision makers and found that doing so reduced ICU LOS among patients who die in the ICU.[15] In both of these analyses, there was no impact on overall mortality, just differences in the choices and circumstances surrounding death.

To understand the impact at a more granular level, consider the results of Ma et al's randomized, controlled trial of formal specialist consultations, which showed a substantial increase in code status changes and in transfers to hospice, along with reductions in ventilator days, number of tracheostomies performed, and rates of postdischarge emergency department visits or readmissions.[16] Taken together, these study results suggest that palliative consultations uncover patient- or surrogate-driven desires to limit aggressive therapies— desires that otherwise may go unrealized. Indeed, it is largely through this improved communication regarding expectations, prognosis, preferences, and resources that palliative medicine programs have been able to reliably boost levels of patient and family satisfaction.

In these studies, the documented benefits of specialty palliative care compared with standard of care (ie, some version of primary palliative care) stem from multiple factors, many of which are structural in nature. Although there may have been some discrepancies in the depth and breadth of knowledge about possible tools in the palliative care toolbox, the observed differences in care patterns that accompanied specialist consultations were likely mediated by more than just clinicians' board certifications. What specialist consultants can also bring to the table is their dedicated time and attention, commodities that are in short supply for primary teams with high patient volume and complexity.

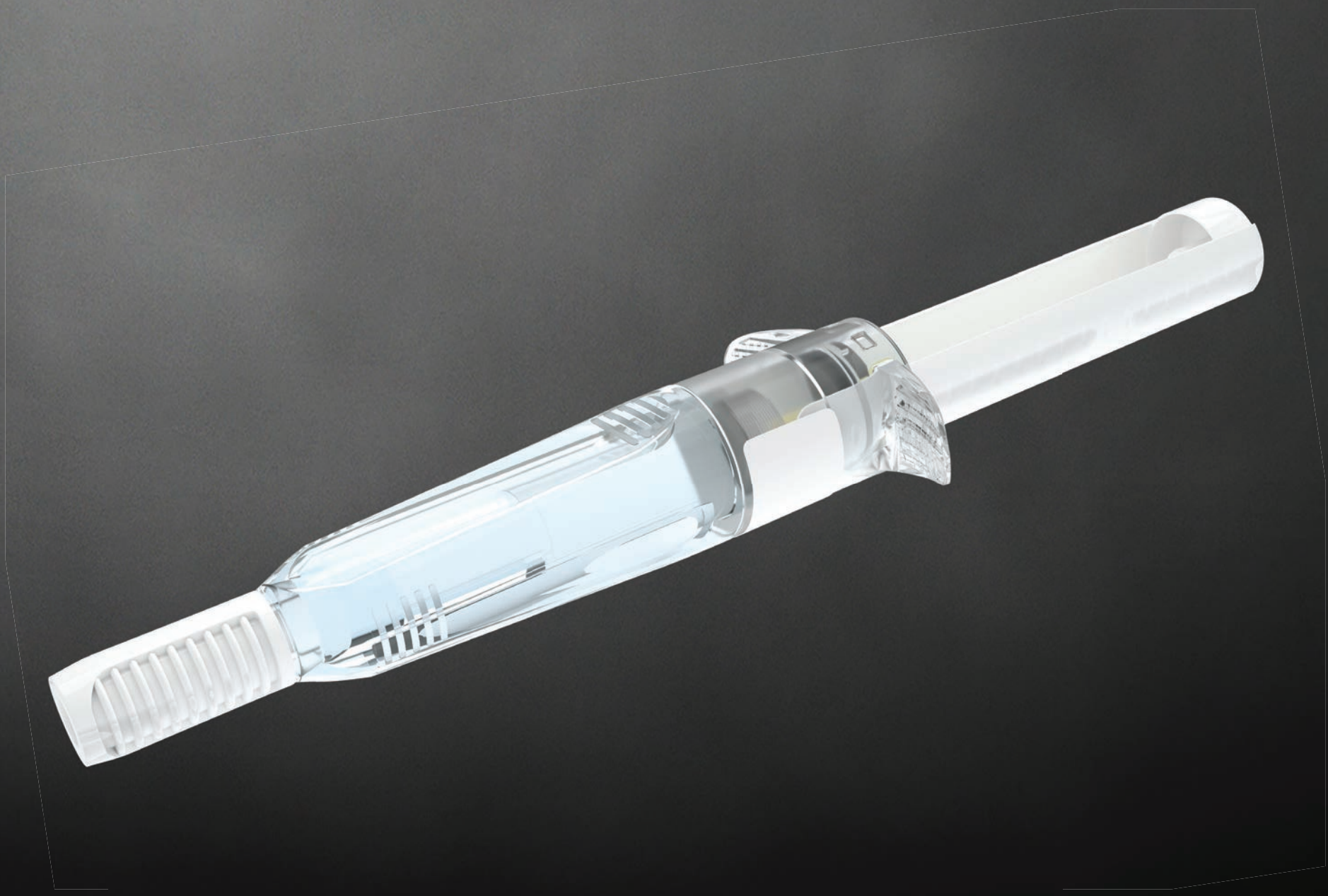
As provider networks strive to expand their palliative services, they will have to determine the circumstances in which primary palliative care will suffice and those in which champion and specialist services would be more efficient and efficacious. With our nation's growing number of seriously ill patients and with the increasing use of predictive analytics, we may begin to lean more on dedicated palliative teams to navigate the ever-important goals of care conversations and the ethics of sharing or withholding life expectancy estimates with the individuals we strive to serve. But whether it is through enlisting primary providers, building the champion workforce, or hiring more specialist consultants, there is no question that palliative programming will need to remain at the heart of our healthcare system's quality transformation. ◆

AUTHOR INFORMATION
MRS is a primary care resident, Duke University School of Medicine; NAB is a research scientist with appointments at the Duke University School of Medicine, Duke's Sanford School of Public Policy and the Durham VA Healthcare System; TWL is a cell therapy and hematologic malignancies specialist and palliative medicine specialist, Duke University School of Medicine and Duke Cancer Institute; KCO, with the Duke University School of Medicine and the Duke Cancer Institute, is the founding director of the DCI Center for Onco-Primary Care and the director of the DCI Supportive Care and Survivorship Center; KIP is with Duke University School of Medicine and the Duke Department of Population Health; JDT is with Duke University School of Medicine; and AHK is with the Duke Cancer Institute and the Duke Fuqua School of Business.

REFERENCES

1. APMs overview. Quality Payment Program/HHS website. qpp.cms.gov/apms/overview . Accessed January 2020.
2. Berwick DM, Nolan TW, Whittington J. The triple aim: care, health, and cost. *Health Aff (Millwood).* 2008;27(3):759-769. doi: 10.1377/hlthaff.27.3.759.
3. Japinga M, Alexander M, Casarett D, Bleser WK, McClellan MB Saunders RS. Slowly getting serious: the new CMS primary care models and implications for serious illness care. *Health Affairs* Blog. https://www.healthaffairs.org/do/10.1377/hblog20190730.120245/full/. Published July 31, 2010. Accessed January 2020.
4. Courtright KR, Chivers C, Becker M, et al. Electronic health record mortality prediction model for targeted palliative care among hospitalized medical patients: a pilot quasi-experimental study. *J Gen Intern Med.* 2019;34(9):1841-1847. doi: 10.1007/s11606-019-05169-2.
5. Bleser WK, Saunders S, Winfield L, et al. ACO serious illness care: survey and case studies depict current challenges and future opportunities. *Health Aff (Millwood).* 2019;38(6):1011-1020. doi: 10.1377/hlthaff.2019.00013.
6. Walling AM, Tisnado D, Ettner SL, et al. Palliative care specialist consultation is associated with supportive care quality in advanced cancer. *J Pain Symptom Manage.* 2016;52(4): 507-514. doi: 10.1016/j.jpainsymman.2016.04.005.
7. Smith S, Brick A, O'Hara S, Nomand C. Evidence on the cost and cost-effectiveness of palliative care: A literature review. *Palliat Med.* 2014;28(2):130-150. doi: 10.1177/0269216313493466.
8. May P, Normand C, Cassel JB, et al. Economics of palliative care for hospitalized adults with serious illness: a meta-analysis." *JAMA Intern Med.* 2018;178(6):820-829. doi: 10.1001/jamainternmed.2018.0750.
9. Milazzo S, Hansen E, Carozza D, Case AA. How effective is palliative care in improving patient outcomes? *Curr Treat Options Oncol.* 2020;5;21(2):12. doi: 10.1007/s11864-020-0702-x.
10. Zimmermann C, Swami N, Krzyzanowska M, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet.* 2014;383(9930):1721-1730. doi: 10.1016/S0140-6736(13)62416-2.
11. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med.* 2010;363(8):733-742. doi: 10.1056/NEJMoa1000678.
12. Kavalieratos D, Corbelli J, Zhang D, et al. Association between palliative care and patient and caregiver outcomes: a systematic review and meta-analysis. *JAMA.* 2016;316(20):2104-2114. doi: 10.1001/jama.2016.16840.
13. Kamal AH, Bowman B, Ritchie CS. Identifying palliative care champions to promote high-quality care to those with serious illness. *J Am Geriatr Soc.* 2019;67(S2):S461-S467. doi: 10.1111/jgs.15799.
14. Kyeremanteng K, Gangon LP, Thavorn K, Heyland D, D'Eqidio G. The impact of palliative care consultation in the ICU on length of stay: a systematic review and cost evaluation. *J Intensive Care Med.* 2018;33(6):346-353. doi: 10.1177/0885066616664329.
15. Bibas L, Peretz-Larochelle M, Adhikari NK, et al. Association of surrogate decision-making interventions for critically ill adults with patient, family, and resource use outcomes: a systematic review and meta-analysis." *JAMA Netw Open.* 2019;3;2(7):e197229. doi: 10.1001/jamanetworkopen.2019.7229.
16. Ma J, Chi S, Buettner M, et al. Early palliative care consultation in the medical ICU: a cluster randomized crossover trial. *Crit Care Med.* 2019;47(12):1707-1715. doi: 10.1097/CCM.0000000000004016.

Somatuline® Depot
(lanreotide) Injection 120 mg



HAVE YOU HEARD ABOUT THE REDESIGNED SYRINGE?

EXPLORE THE FEATURES AT
WWW.SOMATULINEDEPOTHCP.COM

IPSEN
Innovation for patient care

Lack of Clarity on Medicare Advantage Palliative, Other Cancer Care Benefits Limits Consumer Uptake

Ted Knutson and Mary Caffrey

CROOK
Hannah Crook, research assistant, Duke-Margolis Center for Health Policy

BISHOP
Lori Bishop, vice president of Palliative and Advance Care, National Hospice and Palliative Care Organization

CONTINUED FROM COVER

Recently, more upheaval came to hospice providers with coronavirus disease 2019 (COVID-19), which was addressed in the $2.2 trillion fiscal package; the bill included provisions for hospice to be delivered by telehealth and other relief.[3]

Amid this unrest, the need for palliative care and hospice grows, especially for those with cancer. Cancer is the 10th most common condition for MA beneficiaries with 5.1% of all beneficiaries having cancer and 1.3% of all with no other conditions, according to the Medicare Payment Advisory Commission (MedPac), an independent agency set up by Congress to examine issues surrounding Medicare.[4] It is also the second leading cause of death in the nation, asserts the Centers for Disease Control.[5]

Data from CMS show that between 2000 and 2017, the share of Medicare decedents who elected hospice rose from 22.9% to 50.4%, or from 534,000 to 1,492,000. Lengths of stay also jumped, suggesting a need for palliative services whether or not patients are receiving them.[2]

But when people do sign up for MA plans, the co-pays and absence of specific services can cause seniors to forego treatment their physicians say they need. The lack of understanding of what palliative care is can often be the first hurdle.

"Consumers may not be aware their health plan has palliative care services. In the current healthcare environment, there is no standard palliative care benefit. Some MA plans are providing palliative services but there is variation in what that includes. Some programs are more telephonic case management," said Lori Bishop, vice president of Palliative and Advanced Care for the National Hospice and Palliative Care Organization (NHPCO), in an interview with *Evidence-Based Oncology*™.

NHPCO is urging that the confusion be reduced by requiring MA plans to use a standard definition of palliative care, she said. Creating palliative care standards provides guardrails for consumers. "This standardization also protects the plan by ensuring a base level of quality," Bishop said.

The NHPCO executive said she can tell there is also a lot of confusion among consumers about the differences between palliative care and hospice care just from the phone calls she gets

"We need to do a better job of connecting people to the right service at the right time. People are getting connected to palliative care sometimes too late and what they really need is hospice care," said Bishop.

Plans Have Flexibility, but There's Confusion

MA plans gained the authority to offer expanded benefits in 2018, when Congress enacted the Creating High-Quality Results and Outcomes Necessary to Improve Chronic (CHRONIC) Care Act.[6] Palliative care was just one of the expanded services permitted under the act.

Today, MA commercial health plans give payers little more flexibility for cancer care than traditional Medicare, said Regional Cancer Care Associates President and Chief Executive Officer Terrill Jordan, who manages 123 physicians in New Jersey, Maryland, Connecticut, Washington, DC, and Pennsylvania.

The flexibility comes in the ability to offer different types of arrangements, more alternatives for customers. As an example, Jordan told *EBO*™ in an interview that MA plans can offer lower premiums in exchange for higher deductibles.

MA plans can pay for home healthcare for high-risk individuals whom traditional Medicare would not cover. As a way to improve care and lower costs, Jordan said the plans can direct patients to wellness programs to control risk factors for cancer such as diabetes and encourage behaviors that can reduce the incidence and severity of cancer, such as losing weight and eating healthier diets.

But in December 2019, the Duke-Margolis Center for Health Policy confirmed Bishop's observations,[7] reporting that after 2 years only a small number of MA plans were offering palliative care benefits, citing operational challenges and contractual issues. Two years after implementation, the Duke-Margolis study found, only 63 plans offer adult day care services and 58 offer palliative care, including "home-based palliative care.[7]

"Consumers may not be aware their health plan has palliative care services. In the current healthcare environment, there is no standard palliative care benefit. Some [Medicare Advantage] plans are providing palliative services but there is variation in what that includes. Some programs are more telephonic case mangement."

—Lori Bishop,
Vice President, Palliative and Advanced Care,
National Hospice and Palliative Care Organization

The report's coauthor, Duke-Margolis research assistant Hannah Crook, said the confusion is acute.

"There are some general misconceptions about palliative and hospice care. There's a tendency for individuals to think they are the same thing or that you have be near the end of life to receive palliative care," Crook told *EBO*. "It will be important to continue examining how plans are rolling out palliative care benefits and how plans and providers help individuals understand what is being offered under a palliative care benefit."

When it comes to palliative care offerings in MA plans, Crook said there is a wide variability. "One plan may offer a comprehensive suite of services with medical, social, spiritual, and other supports," she explained.

Palliative Care Not Selected

The Duke-Margolis authors noted that starting with their 2019 offerings, MA plans were given new flexibility to offer benefits that improve people's health and ability to live independently, including in-home palliative care, even if those benefits are not traditional medical services.

But the authors found the take-up rate by the plans for palliative care was much smaller than the number one supplemental benefit increased: caregiver support. They predict that in-home palliative care will continue to be a low priority for plans in the starting years of the new flexibility as they set their sights on "low-hanging fruit" that are less costly and easier to deliver.

However, the authors said the detailed offerings of palliative care by plans are not being revealed in initial data.

"For example, one plan may offer a holistic suite of services under its palliative care benefit, including home-based services by specialty-trained palliative care clinicians, a 24/7 call center, a multidisciplinary team with social workers and chaplains, and integrated pain management. Another plan's palliative care benefit may only include more basic services, such as a hospital-based consultation with a clinician (regardless of training) who discusses a person's goals of care," the report states.

Before the advent of the new flexibility in Medicare Advantage, the authors said a palliative care benefit was almost exclusively offered by Medicare-Medicaid Plans, and those that did were steadily declining.

With the CMS change, 15 standard MA plans noted that they offered a "palliative care" benefit, and 8 indicated they offered a "home-based palliative care" benefit in 2019. The numbers increased to 61 (including 58 standard MA plans) plans claiming they offered a palliative care benefit for 2020, with all plans specifying it as "home-based palliative care."

The academics predicted an increase in the number of MA plans offering palliative care services beginning next year. That will be due to another anticipated change: the MA Value-Based Insurance Design (VBID) pilot, which was first presented last year then outlined in a CMS proposal for a carve-in in January.[2]

What Is the MA VBID Pilot?

Right now, when a person with MA coverage needs hospice, a "carve out" provision allows fee-for-service (FFS) Medicare to cover certain services. Hospice providers say the system has worked well, but the CMS website says this results "in a convoluted set of coverage rules for MA enrollees," and that the current system "fragments accountability for care and financial responsibility across the care continuum."[8]

Under the MA VBID initiative, insurers that offer MA plans are required to test wellness and health planning components, and beginning in 2021 they have the option of adding hospice benefits to the Part A package.

Stakeholders have concerns. Long before the disruption of COVID-19, NHPCO had asked for a delay, saying that although the idea for the carve-in makes sense long-term, there was not enough time to prepare for such a major change.[9] There were also complaints that the Center for Medicare and Medicaid Innovation had not offered enough details about what it wanted before MA plans were to apply to take part.

The Duke-Margolis authors see the MA VBID as an improvement, saying plans will be able to offer members a longer continuum of serious illness care, with palliative care preceding hospice. Many MA plan executives they spoke with, especially those with offerings in a number of regional markets, were looking at implementing small-scale pilots.

"This approach allows the plans to carefully monitor implementation and gather data that can inform benefit pricing. If these efforts are successful, they can be brought to scale and to different markets as formal benefits," according to the report.[7]

Ongoing Challenges With MA in Cancer

Whatever the fate of the hospice carve-in, MA plans have their critics, including one oncologist with experience developing alternative payment models.

"If all the Medicare Advantage programs went away tomorrow, I would be thrilled. They have all the disadvantages of commercial insurance without enough money to manage patients," said Barbara L. McAneny, MD, immediate past president of the American Medical Association, who developed the COME HOME oncology care model at the New Mexico Cancer Center.

Prior authorization in MA and all forms of commercial health insurance harms patients, wastes time and money, and creates burdens for medical staff, McAneny said. She has never known an MA plan to deny a request, so the delays prove pointless, serving only to keep patients from getting treatments when they need them. By contrast, Medicare FFS pays quickly and doesn't make oncologists preauthorize all the tests.

"Get rid of prior authorizations. Care should come on systems that are electronic, instant, and evidence-based on medical evidence, not financial evidence," she said.

She also objects to a recent CMS change that allows MA plans to permit step therapy, which allows plans to deny more expensive drugs even if physicians believe they are the most effective. "It's terrible," she said. "Fail first is costing patients quality and quantity of life by using old drugs."

However, America's Health Insurance Plans (AHIP) Vice President for Medicare Policy Greg Berger said MA is one of the nation's most successful healthcare programs with over 23 million participants and a 93% satisfaction rate—satisfaction due to more benefits, better access, and better value to seniors.

He said peer-reviewed research has found MA plans have outperformed the traditional Medicare program on 16 out of 16 clinical quality measures, including breast and colon cancer screening.

Berger acknowledges that prior authorization has flaws, which AHIP wants to cure. The trade group noted most physicians still use manual processes to request prior authorizations, despite the common availability of online submission portals.

In January, AHIP launched the Fast Prior Authorization Technology Highway (Fast PATH) to speed up prior authorization requests, responses, and information exchange. Anthem, Blue Shield of California, Cambia Health Solution's affiliated health plans, Cigna, Florida Blue, and WellCare, who have over 60 million people in their plans, have signed up.[10]

With Surescripts technology, doctors will have critical information at their fingertips when a patient is in the office to help prescribe medications.

"Reducing surprises at the pharmacy counter and making it more likely the patient will receive and take the medication. Together, this should promote better patient outcomes," the AHIP announcement says.

The greatest challenge faced by health plans, providers, and consumers alike with MA plans and cancer care is the rapid increase in drug costs, said Andrew Hertler, MD, chief medical officer at New Century Health.

Spending on cancer drugs in the United States reached nearly $57 billion in 2018, which represented a 2-fold increase from 2013, he said. Cancer care now represents 12% of all costs for Medicare populations and is rising annually at 8% to 10%, said Hertler, who advises on costs for 8000 oncologists in 39 states.

He estimates about one-fourth of cancer patients delay getting a test or treatment due to cost. "Too often I hear stories of patients in Medicare Advantage plans who cannot afford their co-payment for drugs, even though the maximal out of pocket would seem quite modest," he said. ◆

REFERENCES

1. CMS finalizes Medicare Advantage and Part D payment and policy updates to maximize competition and coverage [press release]. Baltimore, MD: CMS newsroom; April 1, 2019. cms.gov/newsroom/press-releases/cms-finalizes-medicare-advantage-and-part-d-payment-and-policy-updates-maximize-competition-and. Accessed March 27, 2020.
2. Center for Medicare and Medicaid Innovation. Introduction to the CY2021 hospice component: VBID model information session. innovation.cms.gov/Files/slides/vbid-hospiceintervention-slides.pdf. Accessed March 27, 2020.
3. Parker J. Senate approves stimulus package with relief for hospices. Hospice News. hospicenews.com/2020/03/26/senate-approves-stimulus-package-with-relief-for-hospices/. Published March 26, 2020. Accessed March 27, 2020.
4. Report to Congress: The Medicare Advantage program: status report. Chapter 13. Published May 2014. medpac.gov/docs/default-source/reports/mar14_ch13.pdf. Accessed March 27, 2020.
5. Centers for Disease Control and Prevention. Leading causes of death. CDC website. cdc.gov/nchs/fastats/leading-causes-of-death.htm. Updated March 17, 2017. Accessed March 27, 2020.
6. S.870. Creating High-Quality Results and Outcomes Necessary to Improve Chronic (CHRONIC) Care Act of 2017. 115th Congress.
7. Crook H, Olson A, Alexander M, Roiland R, Japinga M, Boucher N, Taylor Jr DH, Saunders R. Improving serious illness care in Medicare Advantage: new regulatory flexibility for supplemental benefits. Duke Margolis Center for Health Policy. healthpolicy.duke.edu/sites/default/files/atoms/files/dukereport_supplementalbenefits_for_final_signoff.pdf. Published December 2019. Accessed March 27, 2020.
8. Centers for Medicare and Medicaid Services. Medicare Advantage Value-Based Insurance Design Model. CMS website. innovation.cms.gov/initiatives/vbid/. Updated March 24, 2020. Accessed March 27, 2020.
9. Parker J. Hospice CEOs voice misgivings on Medicare Advantage. Hospice News. hospicenews.com/2020/03/11/hospice-ceos-voice-misgivings-on-medicare-advantage/. Published March 11, 2020. Accessed March 27, 2020.
10. Donaldson C. New Fast PATH initiative aims to improve prior authorization for patients and doctors. Washington, DC: AHIP Newsroom; January 6, 2020. ahip.org/new-fast-path-initiative-aims-to-improve-prior-authorization-for-patients-and-doctors/. Accessed March 27, 2020.

SANOFI GENZYME

NOW APPROVED

SARCLISA®
(isatuximab-irfc)

Injection for IV use | 500 mg/25 mL, 100 mg/5 mL

To learn more and for full Prescribing Information,
visit **sarclisahcp.com**

Scan
to visit

 SAUS.ISX.19.06.3439 03/20