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THE PALLIATIVE CARE SPECIAL ISSUE

Payer Perspective

Patient, Physician, and Payer Conversations in Palliative Care: *Moving Beyond Fear*

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Advances in medical treatment and public health initiatives have contributed to increased life expectancy in the United States. As the population ages, chronic conditions have become the main cause of death for individuals over the age of 65 years.[1] Chronic disease can have a broad range of adverse consequences including social isolation, pain, depression, and impaired functioning. The availability and use of services to improve the quality of life for individuals with chronic or life-limiting illness have not kept pace with the technologic advances that contribute to greater longevity.

The Health and Retirement Study, a longitudinal study that surveys approximately 20,000 individuals over the age of 51 years every 2 years, evaluated trends in pain intensity and symptom prevalence in over 7000 participants who died while enrolled in the study. Between 1998 and 2010, the prevalence of pain, depression, and periodic confusion increased significantly during the last year of life among these patients.[2] These findings are particularly troublesome given the extensive recommendations that resulted from the Institute of Medicine (IOM) report *Approaching Death: Improving Care at the End of Life* published in 1997.[3] The recommendations included research, education, and discussion among healthcare providers, patients, and policy makers to strengthen the knowledge and resources for end of life care.

Palliative care offers a comprehensive, holistic approach to alleviating distressing symptoms in individuals

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Provider Perspective

Trading Conflict for Synergy: *The New Normal for Oncology and Palliative Care*

MICHAEL D. FRATKIN, MD

When the ground shifts under your feet, it's best to shift with it or you will fall…hard. Economic incentives are being turned upside down and a seismic change is approaching. The healthcare system that the current fee-for-service model has spawned will be unrecognizable in 5 years. In times of change like this, it is wise to invest in the future rather than the past. The most important stakeholders—patients, families, and caregivers—have been suffering. Those of us who are professionals dedicated to their well-being, have been suffering too. That's why we built ResolutionCare,[1] a community- based, home-centered palliative care program in rural Northern California. As a palliative care specialist embedded in a community medical oncology program with only 2 oncologists, my professional suffering entailed being overwhelmed with too many consultation requests and very little support. I could only see 1 out of 4 late stage cancer patients referred, which meant constantly triaging to determine who had the most dire symptoms and psychosocial distress. Much of my time was spent choosing which patients with dismal symptoms I would see, and how many nights would I fail to put my children to bed. One morning, I went to wake up my 9-year-old daughter, Bella. When she opened her eyes, she said, matter-of-factly, "Goodbye Daddy."

Nope. Not me. I am not a "goodbye Daddy" Daddy. I knew that something had to change.

What we were missing at our practice

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Cost of Care

The Role of Palliative Care in Accountable Care Organizations

AMY S. KELLEY, MD, MSHS; AND DIANE E. MEIER, MD

Palliative care is specialized medical care for people with serious illness, focused on providing patients with relief from the symptoms, pain, and stress associated with the illness—irrespective of the diagnosis or stage of the disease. The goal is to improve quality of life for both the patient and the family. Palliative care is appropriate at any age and at any stage in a serious illness and is provided concurrent with routine disease treatment.[1]

Accountable Care Organizations (ACOs)—designed to improve quality while containing the cost of care for a defined population of patients—are proliferating in the setting of healthcare reform (**Figure**). Palliative care has become vital to the success of ACOs because of the high concentration of healthcare spending among seriously ill patients and palliative care's ability to improve value (ie, raise quality and reduce costs) for this group. In this paper, we summarize the evidence supporting palliative care's impact on healthcare value, describe the key characteristics of successful palliative care programs integrated with ACOs, and provide a case study of 1 such program.

PALLIATIVE CARE AND THE VALUE EQUATION

In 2011, the United States spent $2.7 trillion on healthcare costs, and projections suggest that by 2040, 1 out of every 3 dollars spent in this country will be used for healthcare.[2,3] Healthcare spending is highly concentrated among a small seriously ill population, whereby 5% of the sickest and most complex patients account for 60% of

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Also in This Issue…

imbruvica®
(ibrutinib) 140mg capsules

DISCOVERING HOW FAR THERAPY CAN GO

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. 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 have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 26% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA®. Monitor patients for fever and infections and evaluate promptly.

Cytopenias - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with IMBRUVICA®. Monitor complete blood counts monthly.

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

Second Primary Malignancies - Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11%).

IMBRUVICA® (ibrutinib) is the first and only FDA-approved therapy for use in patients with Waldenström's macroglobulinemia (WM)

IMBRUVICA® is approved for use in 4 indications

IMBRUVICA® is indicated for the treatment of patients with

Mantle cell lymphoma (MCL) who have received at least one prior therapy.
Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

Chronic lymphocytic leukemia with 17p deletion.

Waldenström's macroglobulinemia (WM).

Tumor Lysis Syndrome - Tumor lysis syndrome has been reported with IMBRUVICA® therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

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®. 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 (≥25%) in patients with B-cell malignancies (MCL, CLL, WM) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, bruising, nausea, upper respiratory tract infection, and rash. Seven percent of patients receiving IMBRUVICA® discontinued treatment due to adverse events.

DRUG INTERACTIONS

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

CYP3A Inducers - Avoid co-administration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment - Avoid use in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA® dose.

Please review the Brief Summary of full Prescribing Information on the following page.

To learn more, visit
www.IMBRUVICA.com

1/15 PRC-00811

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Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)
IMBRUVICA® (ibrutinib) capsules, for oral use
See package insert for Full Prescribing Information

INDICATIONS AND USAGE

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

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

Chronic Lymphocytic Leukemia: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy *[see Clinical Studies (14.2) in Full Prescribing Information].*

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

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies.

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

Infections: Fatal and non-fatal infections have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 26% of patients. *[See Adverse Reactions].* Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA. Monitor patients for fever and infections and evaluate promptly.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with IMBRUVICA.

Monitor complete blood counts monthly.

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

Second Primary Malignancies: Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11 %).

Tumor Lysis Syndrome: Tumor lysis syndrome has been reported with IMBRUVICA therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL and 20 times those reported in patients with CLL or WM, receiving the ibrutinib dose of 560 mg per day and 420 mg per day, respectively. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking IMBRUVICA. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations].*

ADVERSE REACTIONS

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

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

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.

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

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

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

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

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

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

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administrative site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3

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

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 2: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MCL (N=111)

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

* Based on laboratory measurements and adverse reactions

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

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

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

Chronic Lymphocytic Leukemia: The data described below reflect exposure to IMBRUVICA in an open label clinical trial (Study 1) that included 48 patients with previously treated CLL and a randomized clinical trial (Study 2) that included 391 randomized patients with previously treated CLL or SLL.

The most commonly occurring adverse reactions in Study 1 and Study 2 (≥ 20%) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, upper respiratory tract infection, rash, nausea, and pyrexia.

Approximately five percent of patients receiving IMBRUVICA in Study 1 and Study 2 discontinued treatment due to adverse events. These included infections, subdural hematomas and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of patients.

Study 1: Adverse reactions and laboratory abnormalities from the CLL trial (N=48) using single agent IMBRUVICA 420 mg daily occurring at a rate of ≥ 10% are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL (N=48) in Study 1

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	63	4
	Constipation	23	2
	Nausea	21	2
	Stomatitis	21	0
	Vomiting	19	2
	Abdominal pain	15	0
	Dyspepsia	13	0
Infections and infestations	Upper respiratory tract infection	48	2
	Sinusitis	21	6
	Skin infection	17	6
	Pneumonia	10	8
	Urinary tract infection	10	0
General disorders and administrative site conditions	Fatigue	31	4
	Pyrexia	25	2
	Peripheral edema	23	0
	Asthenia	13	4
	Chills	13	0
Skin and subcutaneous tissue disorders	Bruising	54	2
	Rash	27	0
	Petechiae	17	0
Respiratory, thoracic and mediastinal disorders	Cough	19	0
	Oropharyngeal pain	15	0
	Dyspnea	10	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	27	6
	Arthralgia	23	0
	Muscle spasms	19	2
Nervous system disorders	Dizziness	21	0
	Headache	19	2
	Peripheral neuropathy	10	0
Metabolism and nutrition disorders	Decreased appetite	17	2
Neoplasms benign, malignant, unspecified	Second malignancies*	10*	0
Injury, poisoning and procedural complications	Laceration	10	2
Psychiatric disorders	Anxiety	10	0
	Insomnia	10	0
Vascular disorders	Hypertension	17	8

**One patient death due to histiocytic sarcoma.*

Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL (N=48) in Study 1

	Percent of Patients (N=48)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	71	10
Neutrophils Decreased	54	27
Hemoglobin Decreased	44	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions

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

Table 5: Non-Hematologic Adverse Reactions ≥ 10% Reported in Study 2

System Organ Class ADR Term	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and administration site conditions				
Fatigue	28	2	30	2
Pyrexia	24	2	15	1
Infections and infestations				
Upper respiratory tract infection	16	1	11	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

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

Table 6: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Study 2

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

* Based on laboratory measurements per IWCLL criteria

Waldenström's Macroglobulinemia

The data described below reflect exposure to IMBRUVICA in an open label clinical trial that included 63 patients with previously treated WM.

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

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

Adverse reactions and laboratory abnormalities described below in Tables 7 and 8 reflect exposure to IMBRUVICA with a median duration of 11.7 months in the WM trial.

Table 7: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (N=63)

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0

IMBRUVICA® (ibrutinib) capsules

Table 7: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (N=63) (continued)

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
Infections and infestations	Upper respiratory tract infection	19	0
	Sinusitis	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

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

Table 8: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with WM (N=63)

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

* Based on laboratory measurements.

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.
Hypersensitivity reactions including anaphylactic shock (fatal), urticaria, and angioedema have been reported.

DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

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

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

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

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

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction *[see Clinical Pharmacology (12.3) in Full Prescribing Information].*

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category D *[see Warnings and Precautions].*

Risk Summary: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. 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.

Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at oral 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 post-implantation loss. The dose of 80 mg/kg/day in animals is approximately 14 times the exposure (AUC) in patients with MCL and 20 times the exposure in patients with CLL 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 animals is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Nursing Mothers: It is not known whether ibrutinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IMBRUVICA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

Geriatric Use: Of the 111 patients treated for MCL, 63% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), infections (pneumonia and cellulitis) and gastrointestinal events (diarrhea and dehydration) occurred more frequently among elderly patients.

Of the 391 patients randomized in Study 2, 61% were ≥ 65 years of age. No overall differences in effectiveness were observed between age groups. Grade 3 or higher adverse events occurred more frequently among elderly patients treated with IMBRUVICA (61% of patients age ≥ 65 versus 51% of younger patients) *[see Clinical Studies (14.2) in Full Prescribing Information].*

Of the 63 patients treated for WM, 59% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), and infections (pneumonia and urinary tract infection) occurred more frequently among elderly patients.

Renal Impairment: Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with Creatinine clearance (CLcr) > 25 mL/min. There are no data in patients with severe renal impairment (CLcr < 25 mL/min) or patients on dialysis *[see Clinical Pharmacology (12.3) in Full Prescribing Information].*

Hepatic Impairment: Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. The safety of IMBRUVICA has not been evaluated in patients with hepatic impairment.

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

Females and Males of Reproductive Potential: Advise women to avoid becoming pregnant while taking IMBRUVICA because IMBRUVICA can cause fetal harm *[see Use in Specific Populations].*

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

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

- *Hemorrhage:*
  Inform patients of the possibility of bleeding, and to report any signs or symptoms (blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions].*
- *Infections:*
  Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Warnings and Precautions].*
- *Atrial Fibrillation:*
  Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions].*
- *Second primary malignancies:*
  Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions].*
- *Tumor lysis syndrome:*
  Inform patients of the potential risk of tumor lysis syndrome and report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions].*
- *Embryo-fetal toxicity:*
  Advise women of the potential hazard to a fetus and to avoid becoming pregnant *[see Warnings and Precautions].*
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day *[see Dosage and Administration (2.1) in Full Prescribing Information].*
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose *[see Dosage and Administration (2.5) 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].*
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"Worldwide, lack of access to effective pain relief and palliative care is responsible for a tremendous amount of unnecessary suffering." -Megan O'Brien, PhD

Initiating the Conversation on Palliative Care, and Introducing Our New Editor in Chief

As quality-of-life discussions become increasingly mainstream in cancer care, patients and physicians are embracing palliative care in their treatment plans. The conversation on end-of-life choices and patient care in hospice settings, patient and caregiver goals, improved pain management, coping with psychosocial stress, has been gradual in acceptance. An open dialogue among the physician (an oncologist when it comes to a cancer patient), the patient, and his or her family on treatment options, goals of care, and patient understanding of treatment outcomes is important for shared decision making. Palliative care needs to be a team effort, and early integration of a palliative care physician into the team (of medical oncologist, radiation oncologist, oncology nurse, the patient's primary care physician, and others) helps put the patient's treatment goals front and center and can definitely improve health outcomes.

In this issue, we bring you some excellent perspectives—from providers of care, a medical director representing a health plan, and a foundation that provides financial and other supportive care to cancer patients—on the benefits of palliative care to the patient, to the caregiver, to the provider, and to society as a whole.

As Drs Amy S. Kelley and Diane E. Meier from the Icahn School of Medicine point out in their article on palliative care in accountable care organizations, "Research has demonstrated that the improved quality of care associated with palliative care leads to lower costs by preventing symptom crises, reducing depression, supporting family caregivers, and matching treatments with patient priorities."

A recurring challenge cited by several authors in this issue is the lack of training of medical students in initiating conversations on treatment goals and palliative care with their patients, and the discomfort they feel in this unknown territory. In their article, Dr Thomas J. Smith, program director of palliative care at Johns Hopkins School of Medicine, and his coauthors inform us about measures being implemented at Johns Hopkins to change the outlooks of both patients and providers. Additionally, they recommend a framework to help physicians guide palliative care conversations.

Equally important is reimbursing palliative care physicians and the procedures, and payers are coming on board as well. We hear from Dr Randall Krakauer, who helped design Aetna's Compassionate Care Program, launched in 2004. While providing her perspective on integrating palliative care into regular oncology care, Dr Patti Forest, senior medical director at Blue Cross Blue Shield of North Carolina, writes, "Blue Cross Blue Shield of North Carolina developed the Blue Quality Physician Program to recognize and financially reward practices that demonstrate a commitment to patient-centered care and focus on improving health outcomes and reducing cost of care."

We are very excited to announce an addition to our team at *The American Journal of Managed Care*. Dr Joseph Alvarnas, associate clinical professor and director of medical quality and quality, risk, and regulatory management, City of Hope, will lead *Evidence-Based Oncology* as its new editor in chief. Dr Alvarnas attended medical school at the University of California, San Francisco. Following his training in internal medicine and fellowships in hematology and hematopoietic cell transplantation at Stanford University Medical Center, he started work at City of Hope, where he was responsible initially for establishing the Banner Transplant Program. He subsequently served as director of the Hematopoietic Stem Cell Processing Laboratory and chair of the quality committee for the transplant program. He is the national co-chair for 2 Bone Marrow Transplant Clinical Trials Network clinical trials, studying stem cell transplantation in HIV-infected patients. Dr Alvarnas serves on the American Society of Hematology (ASH) Committee on Practice and as an ASH liaison to the Committee on Quality.

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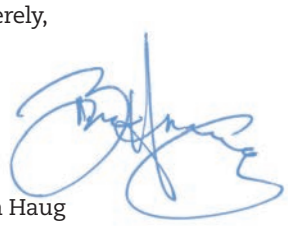

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EDITORIAL MISSION

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

Palliative Care Integrates Value in Cancer Care

Joseph Alvarnas, MD

ABOUT THE EDITOR IN CHIEF

JOSEPH ALVARNAS, MD

Joseph Alvarnas, MD, is associate clinical professor and director of medical quality and quality, risk, and regulatory management, City of Hope, Duarte, CA.

Over the past 4 decades, cancers survival rates have improved significantly. The American Association of Cancer Research estimates that 1 of 22 people living in the United States is a cancer survivor, bringing the total to nearly 14.5 million current survivors. As an oncologist specializing in the care of patients with blood cancers, I have seen patients affected by many previously untreatable diseases live longer, healthier, better-quality lives thanks to a rapidly evolving armamentarium of innovative and targeted therapies.

Much of the national conversation regarding cancer care now focuses upon how best to deploy these new agents, how to ensure adequate access to best-practice–based medicine, how to be a good steward to the increasingly expensive portfolio of anticancer medications, and how to ensure the functional and economic sustainability of our healthcare system.

In this inexorable push toward more innovative cancer care, it is easy to forget that not all patients can be cured. As physicians, there is a certain internal reassurance in being able to offer our patients more—1 more chemotherapeutic regimen, another novel therapeutic agent, and another attempt at radiation therapy. In our zeal to offer something more, we may sometimes forget how best to honor the priorities and needs of our patients. In those conversations that are most difficult to have, redefining the goals of care for someone who cannot be cured may form the basis for the most powerful therapy possible.

The idea of actively assisting patients throughout this process falls outside of our traditional disease-based treatment models. Palliative care physicians provide oversight and expertise to insure the proper care and management of distress, pain, emotional suffering, coping, end of life, grief, and recovery. The discipline incorporates psychosocial and spiritual care according to patient and family needs, values, beliefs, and culture. The goal of palliative care is to anticipate, prevent, and reduce suffering in order to ensure the best possible quality of life for patients and their families.

Palliative care is most effective when it is engaged early in the care of patients—it can help provide extraordinary value to patients affected by cancer by shifting the care model from being disease-and-organ–focused to being patient-and-family–centered. Too often, palliative care physicians are called in when it is too late to adequately address issues of suffering, end-of-life care, and end-of-life decision making.

In this issue of *Evidence-Based Oncology*, we explore in depth the topic of palliative care. The authors review not only how to make such care more accessible, but how to better understand the extraordinary value that is delivered by making palliative care an integral part of our cancer care delivery models. As cancer care is increasingly metricized, we need to ensure that we develop metrics adequate to afford appropriate value to palliative care.

Twenty years ago, my father was diagnosed with incurable colon cancer. His physician introduced our family to palliative care. In so doing, he ensured the best possible care for my father and our entire family. I have come to believe that the best measure of the effectiveness of our fight against cancer is not the number of genes that we have sequenced, or studies that we have performed, or new medicines that have been created; it is our ability to restore hope to someone who is suffering from the fear of a new cancer diagnosis, it is our ability to help a family affected by cancer find a sense of wholeness, and it is our ability to center our care on the most pressing needs of our patients and their families. **EBO**

NCCN 2015: Reviewing the Past to Build the Future

Joseph Alvarnas, MD

The 20th Annual Conference of the National Comprehensive Cancer Network (NCCN) in Hollywood, Florida, offered an opportunity to take stock of the profound advances in the standards of care for a number of cancers over the past 2 decades. During this period, our expectations about the treatment and prognosis of many cancers have been upended by our growing understanding of small molecules, molecularly targeted therapeutics, monoclonal antibodies, and immunotherapeutic technologies.

Some of the most extraordinary of these advances have occurred in the care of patients with blood-based cancers. Breakout sessions on chronic myelogenous leukemia (CML), chronic lymphocytic leukemia, and multiple myeloma (MM) illustrated the importance of targeted therapeutics, monoclonal antibodies, and innovative combination therapies in the treatment of these diseases. For CML and MM in particular, the new therapeutic approaches have dramatically improved survival rates and completely altered the standards of care for these diseases in ways that were unimaginable 20 years ago.

Breakout sessions on the care of patients with breast cancer, small cell lung cancer, non-small cell lung cancer, and ovarian cancer highlighted our marked progress in the care of patients affected by these diseases. Many of these sessions focused on risk-adapted strategies for best utilizing surgery, novel radiotherapeutic approaches, adjuvant and neoadjuvant chemotherapy, biologically targeted agents, and use of monoclonal antibodies to improve clinical effectiveness and limit toxicity to patients. One highlight was a primer for patients on the biology of evolving immunotherapeutic technologies. Issues of survivorship and therapy-related toxicity were also addressed through sessions on fertility preservation and prevention of treatment-related cardiac toxicity.

In addition to providing an excellent foundation for better understanding the biology and the clinical standards of care for managing many patients with cancer, this meeting was striking in that the NCCN highlighted the importance of addressing issues of value, efficiency, and the need for systemic change in how we approach the evolving healthcare system. In the post Affordable Care Act world, it is not enough to talk about cancer treatment without entering into a broader conversation about how to fulfill the challenges of healthcare reform and ensure the sustainability of our care delivery system. This topic was addressed directly by Robert Carlson, MD, in his keynote address, "20 Years of Improving the Quality, Effectiveness, and Efficiency of Cancer Care," and in a roundtable discussion on improving cancer care and value-based decision making. NCCN leaders made it clear that it was not enough to talk about best practice: it must be discussed in the context of the broader national issue of value delivery in cancer care.

Part of the challenge the NCCN faces, in addition to ensuring that the clinical practice guidelines are current, is ensuring their continuing relevance as a tool for enhancing value delivery in healthcare. Issues of how best to exercise stewardship of an increasingly expensive armamentarium of novel cancer therapeutics, and how to ensure that those practicing in resource-limited settings are able to offer effective care, are among the challenges facing the NCCN.

The NCCN Practice Guidelines in Oncology represent a robust set of tools that assist in the care of patients whose treatment choices are increasingly complex. The 20th Annual Meeting was an opportunity both to celebrate the great achievements of the past 2 decades and to contemplate the enormous tasks that lie ahead. **EBO**

A Need for More, Better, and Earlier Conversations With Cancer Patients About Goals of Care

Rachelle Bernacki, MD, MS; and Ziad Obermeyer, MD, MPhil

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A recent study of Medicare beneficiaries with poor-prognosis cancers found statistically significant differences in care utilization between hospice and non-hospice beneficiaries at the end of life.[1] While enrolled in hospice, beneficiaries were hospitalized less, received less intensive care, underwent fewer procedures, and were more likely to die at home—consistent with the preference of most patients. In order to realize the benefits of hospice, however, a clinician-patient discussion about goals of care—in the context of serious illness—must occur early in patient care.

If end-of-life (EOL) discussions were pharmaceutical agents, they would be blockbusters. EOL discussions result in 37.5% lower costs among patients, and patients with higher costs had worse quality of life in their final week.[2] Increasing the practice of early EOL discussions has been proposed as one of 5 key changes that can "bend the cost curve" in oncology care.[3] In short, we need more, better, and earlier conversations about goals of care for patients with advanced cancer.

Unfortunately, evidence suggests that EOL conversations occur infrequently, and that even when they do they are inadequate.[4] A study to assess psychosocial coping of patients with cancer found that EOL discussions did not occur regularly; indeed, only a third of the population of dying patients reported having discussed EOL issues with their physicians, at 4 months before death on average.[5] When these talks did occur, they resulted in less aggressive medical care near death and earlier hospice referrals.[5]

BARRIERS TO CONVERSATIONS

Why are more, better, and earlier conversations about goals of care not the norm for patients with advanced cancer? Physician discomfort with discussing advance care planning (ACP) is likely a result of inadequate training. This lack of training is a major obstacle to better and more effective discussions.[6] Oncologists often need to communicate bad news to patients, but very few oncology training programs instill the essential psychosocial skills required for optimal care of cancer patients and/or their families, and fellows describe significant gaps in their confidence and competence in addressing key EOL issues. Oncologists deliver bad news to patients an average of 35 times a month,[7] yet a national survey documented that few oncology trainees report training or mentoring in communication skills such as discussing a prognosis with a patient.[8]

The outcome? Conversations on patient preferences for future care tend to be short. One study described how physicians' discussions with patients of advance directives lasted 5.6 minutes.[9] According to the study, physicians tend to speak for the majority of the time, and the discussion is usually focused on preferences for technical interventions rather than the patient's goals for care.[9] Because patients' goals and values are not explored in detail and the physician provides insufficient information and recommendations about the use of technologies in achieving patient goals, decisions may not necessarily reflect patients' true wishes. Since conversations about serious illness care goals are difficult, stressful, and emotionally challenging for both physicians and patients,[10] using a structured guide can support clinicians and assure completion of key steps in the conversations.[4]

Second, evidence suggests that physicians have difficulty formulating and communicating prognosis—a prerequisite for appropriately timed conversations. If providers do not clearly communicate, in an understandable way, that death is approaching, patients will be unable to factor that information into the decisions they make. A national survey found that while 90% of physicians believed they should avoid specifics about prognosis, 57% felt inadequately trained in prognostication.[11] Another study, evaluating the accuracy of physician prognostic skills, asked physicians to provide survival estimates of terminally ill patients at the time of hospice referral. Physicians were accurate only 20% of the time and were biased toward overestimation of survival by a factor of 5.3.[12] Importantly, patient understanding of prognosis significantly influences their decisions about aggressiveness of care. A study of older patients (>75 years) and those with chronic disease (>65 years) indicated that fewer patients that were aware they had a terminal illness sought complicated and invasive treatments.[13] The overwhelming majority of patients want to discuss their prognosis with physicians, and inadequate prognostic information is one of the most cited complaint patients and families have about EOL care.[14] However, patients often do not receive all the information they need in order to make choices consistent with their values and desires.[14]

While difficulties with prognostication may be partly responsible for a decrease in the average length of stay in hospice, the use of hospice for the care of terminally ill patients has increased 10-fold—from 158,000 patients in 1985 to over 1.53 million in 2012.[15] Fifteen percent of hospice patients are referred in their last week of life, when benefits to the patient and family may be limited.[15,16] In a recent study, the median length of hospice stay for patients with lung cancer was 4 days.[17] However, families feel they receive greater benefit from longer lengths of stay in hospice.[18] Future efforts to define an "optimal" length of stay in hospice should consider patients' and families' perceptions of the benefits that hospice offers.

Timing is also critically important for conversations about goals of care. Choosing the appropriate time for patients with serious illness to have this conversation can have a profound impact on the value of ACP efforts.[19] Advance directives that are completed too early or too late can lead to EOL decisions that may not reflect the patient's values, goals, and preferences. Palliative care specialists practice and support the concept of "just in time" decision making.[20] Rather than making final decisions regarding future care and interventions, the goal should be to encourage earlier EOL communication that prepares the patient, his or her family members, and clinicians to make better decisions when questions arise in the future. In this way, "just in time" decision making avoids some of the possible undesirable outcomes of ACP,[21] such as premature decisions made without sufficient information.

SYSTEM IMPROVEMENT NEEDED

Building on our understanding of these obstacles, we need to ensure that more goals of care conversations happen, and that they happen at the right time. Making certain of this is critical to promoting the high-value (best for the lowest cost) care that hospice can help provide. To reach this goal, several steps need to be realized.

First, systems need to identify patients at high risk of facing EOL decisions, and then highlight these patients as those who could potentially benefit from additional intervention.[22] This allows clinicians and institutions alike to target resources such as care management, geriatric, and palliative care consultation to those who most likely need them, rather than being at the whim of the referring clinician, who may or may not be familiar with those resources. However, limited access to specialist palliative care prevents the full realization of its benefits, as a shortage of board-certified physicians in hospice and palliative medicine is a major barrier to access.[23]

Second, to overcome this shortage, generalist physicians should be trained to develop competencies to practice primary palliative care, with backup and support from palliative care specialists.[24] While primary palliative care includes basic discussions about prognosis and goals of treatment, specialist palliative care teams provide assistance with conflict resolution regarding goals or methods of treatment within families, between staff and families, and among treatment teams.[24] However, since generalist physicians have noted a

lack of training and comfort with conducting early ACP discussions, there is an urgent need to adequately train them to conduct goals-of-care conversations. In the absence of a funded mandate to provide training to generalists to conduct patient-centered conversations about goals of care for the seriously ill, some institutions, particularly accountable care organizations, are investing in training non–palliative care physicians to develop generalist-level palliative care competencies.[25] Such resource investment helps insure that all patients have access to palliative care services, and consequently that palliative care specialists can focus on patients with complex needs while direct, basic palliative care services are provided to most patients by generalist physicians.

Finally, it should be easy to find information in the electronic medical record (EMR) about patients' values, goals, and preferences for care, as well as other key information, including healthcare proxy, Medical Orders for Life-Sustaining Treatments forms, and code status. Currently, in many systems, this vital information is scattered and difficult to find. In order to accelerate improvement, the simple assessment of the presence of ACP information is unlikely to be adequate—indicators of quality of discussion are essential and need to be developed. In addition, making a section in the EMR a "single source of truth" for documentation of patient values and goals-of-care conversations would allow for performance standards to be developed; clinicians and systems would be accountable for the care provided,[26] including key indicators related to discussion and documentation of serious illness care goals.

To realize the goal of more, better, and earlier discussions with patients about care goals, we should begin by focusing our attention on these 3 areas: 1) education of clinicians; 2) identification of appropriate patients; 3)user-friendly, structured sections in the EMR for recording information; and 4) continuous measurement of performance. **EBO**

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POLICY

Creating Value-Based Metrics for Cancer Care: A Stakeholder-Informed, Evidence-Driven Approach

Scott D. Ramsey, MD, PhD; and Gary H. Lyman, MD, MPH

INTRODUCTION

The cost of cancer care is one of the fastest growing components of healthcare spending in the United States, with expenditures expected to increase from $125 billion in 2010 to an estimated $158 billion in 2020.[1] With recognition that there is varying and often suboptimal use of costly cancer care services, several groups have called for interventions to enhance the value of cancer care by improving outcomes while maintaining or reducing costs faced by patients, payers, and society.[2-5] Efforts to improve value will entail establishing metrics that capture value, implementing programs to improve value, and tracking trends over time. However, agreeing on the definition of "value" in cancer care, and how it should be measured, is a potentially contentious process. With these issues in mind, we describe a multistakeholder, data-driven, research-enabled regional network that is focused on defining, measuring, and improving value in cancer care for patients, their families, and society. We believe that our "bottom-up" regional strategy may provide a model for developing, implementing, and evaluating promising interventions aimed at improving cancer care.

THE VALUE IN CANCER CARE INITIATIVE

In 2013, the Fred Hutchinson Cancer Research Center's Hutchinson Institute for Cancer Outcomes Research (HICOR) established a regional consortium consisting of cancer care providers, payers, patient advocates, and researchers committed to improving outcomes and reducing costs of cancer care: the Value in Cancer Care Initiative. The rationale for the multistakeholder process is grounded in theory and experience that a change in practice is best achieved by direct participation by those who are impacted and who have both control of, and a stake in, the process.[6-10] A steering committee with representatives from the stakeholder groups organized a regionwide meeting to introduce the concept of improving value in cancer care. The meeting, held in January 2014, included nearly 70 individuals representing 20 organizations from across the region.[11] The meeting organizers tasked this group with identifying 3 to 5 metrics capable of measuring "value" from their perspective. Rather than focus on a single definition of value,[12] the organizers asked stakeholders to consider their own definition of value, with the caveat that a value metric must minimally consider costs and clinical outcomes from their perspective as patients, payers, or providers. Additionally, attendees were informed that the value metrics should be both *meaningful* from their perspective—ie, represent issues that improve either the efficiency of care, or the lives of cancer patients, or both—as well as *actionable*, meaning amenable to intervention

(continued on page **SP170**)

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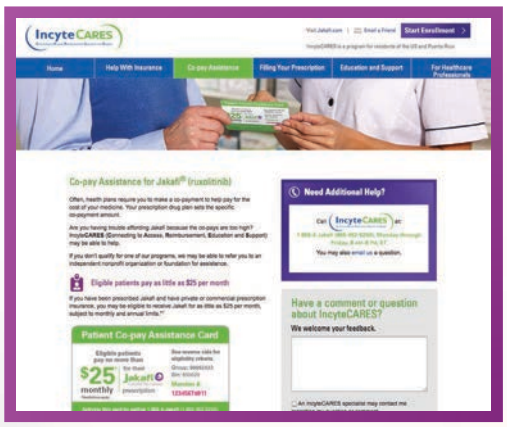

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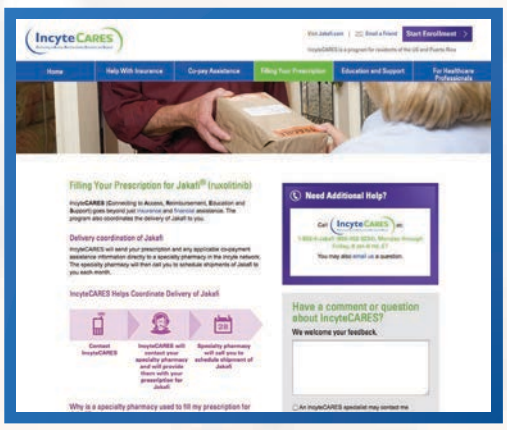

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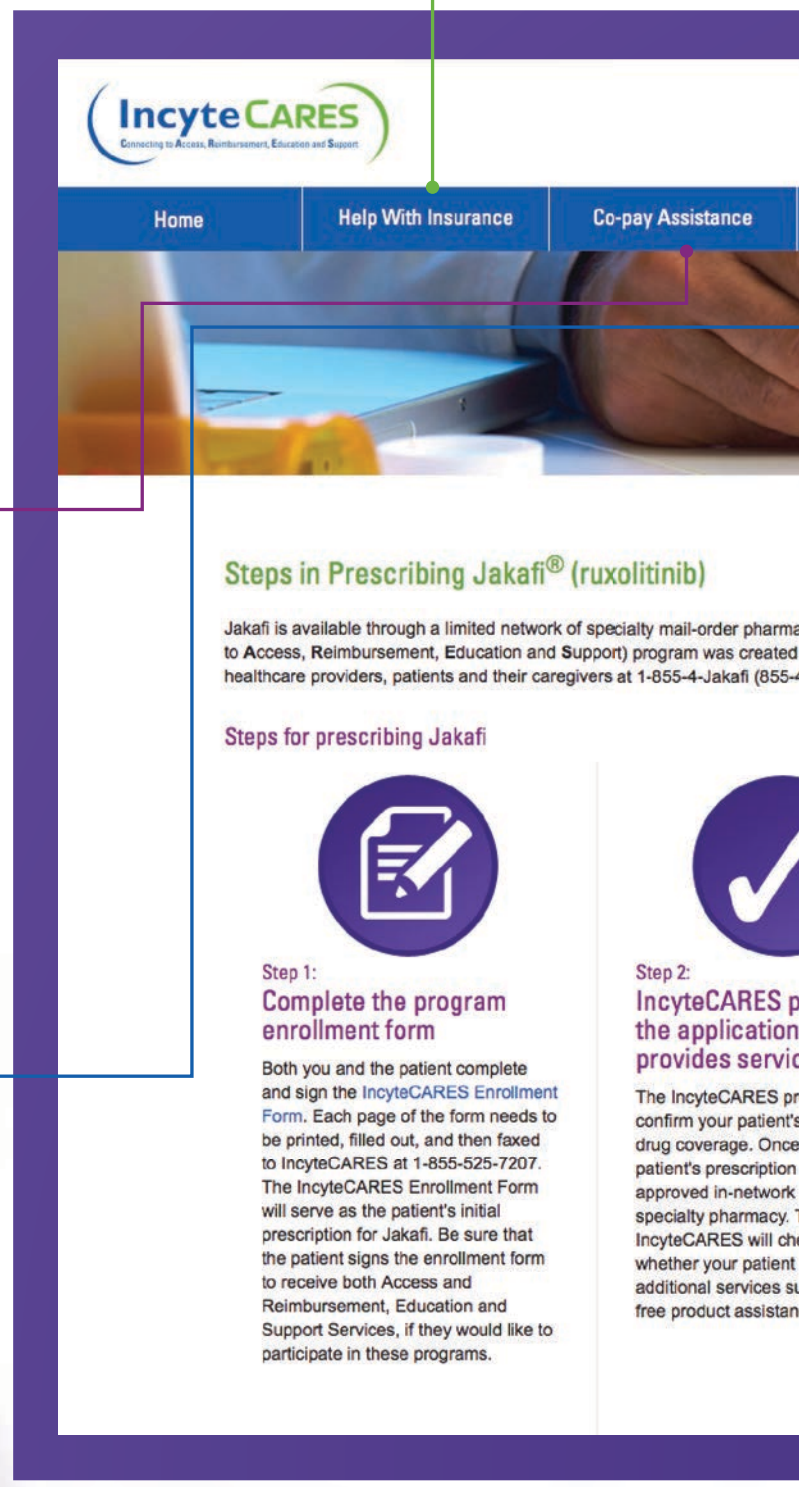

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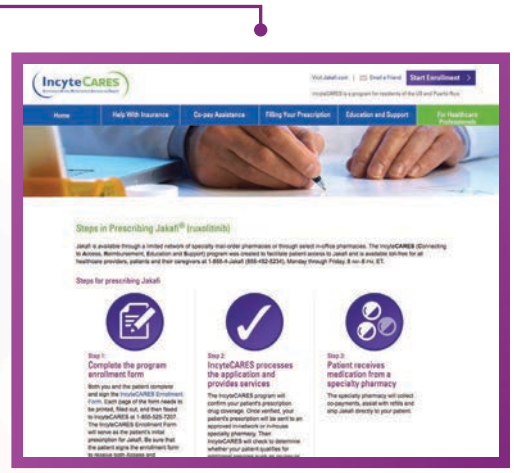
Enrollment

To enroll patients in the IncyteCARES (Connecting to Access, Reimbursement, Education and Support) program, both the patient and doctor must complete an enrollment form. Download a copy of the enrollment form, fill it out with the patient, and fax the form to IncyteCARES at 1-855-525-7207.



For Healthcare Professionals

Learn the necessary steps that must be taken when prescribing Jakafi to patients, and discover the resources that the IncyteCARES (Connecting to Access, Reimbursement, Education and Support) program makes available to you and your patients.

Education and Support

Discover how the IncyteCARES (Connecting to Access, Reimbursement, Education and Support) program provides education and information on Jakafi to help patients take a proactive approach in their care and work more effectively with their doctors.

Jakafi™ ruxolitinib (tablets)

IncyteCARES
Connecting to Access, Reimbursement, Education and Support

(continued from page SP167)

within the healthcare system. Importantly, the organizers stressed that it should be feasible to generate the metrics without undue burden on any 1 stakeholder group. It would be the task of HICOR to create the final metrics and report back on them at the next summit.

During the conference, multistakeholder "working groups" independently created lists of possible value measures across 3 phases of cancer care: treatment, survivorship, and end of life. Although approximately 750 metrics within 9 domains were initially offered by the working groups, a final prioritization exercise involving the full group identified 6 domains as standouts on the 2 dimensions of meaningfulness and actionability (**FIGURE**).

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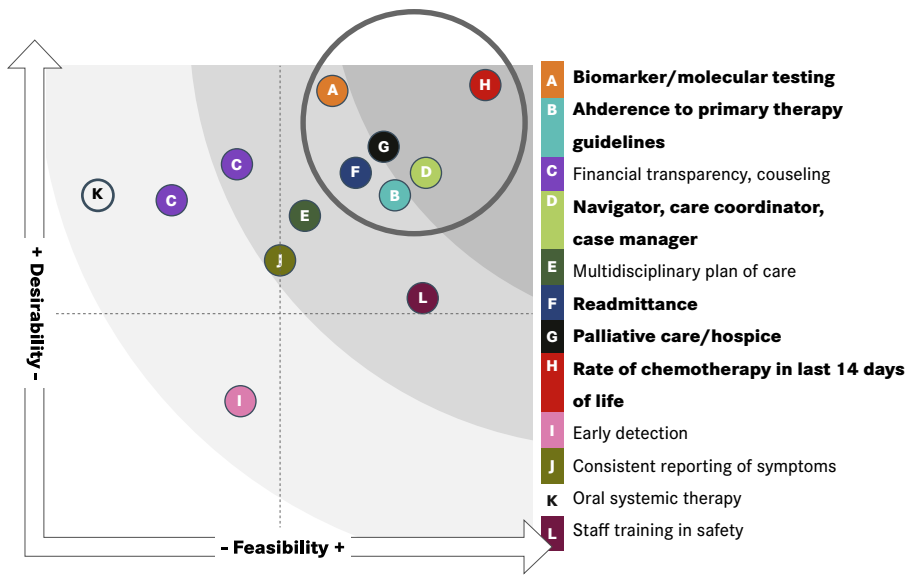
LESSONS LEARNED: KEY ELEMENTS OF THE STAKEHOLDER ENGAGEMENT MODEL FOR GENERATING VALUE METRICS

The aspirational goal of improving outcomes in cancer care while reducing costs confronts the reality that while diverse stakeholder groups must work together to achieve this goal, they may have competing or even diametrically opposed interests and goals. A health insurer's cost can be a clinician's revenue; patients may distrust the actions of insurers and even physicians to restrict "unnecessary" care if they feel it threatens their options or potential well-being. Therefore, the necessary task of trying to achieve concordance on which metrics are worthy of attention and support is often delegated "top-down" from a single stakeholder group, creating antagonism early in the process and ultimately reducing the likelihood of achieving constructive change. We have outlined several aspects of our process, listed below, that we believe are replicable in other regions and that may increase the likelihood of implementation and ultimately positive change. The latter goal remains to be proved.

1. **Bottom-up multistakeholder engagement in all phases of the process:**
   - Defining relevant clinical questions
   - Selecting specific metrics
   - Defining measurement algorithms
   - Selecting potential interventions to improve care where the value is low
2. **Emphasis on actionable and meaningful metrics.** Actionable measures create near-term opportunities to improve outcomes and lower costs. Meaningful metrics provide all stakeholder groups with the opportunity to support them from the perspective of their own organization. The most meaningful metrics are self-apparent (eg, survival) and thus require less translation when tools have been developed to capture them, summarize the results, and disseminate the findings. Other metrics require translation, which should be done from the patient's perspective. For example, "chemotherapy at the end of life" might be better referred to as "overtreatment," to convey the notion that the treatment does not improve quantity or quality of life.
3. **Willingness to accept some metrics that might not be personal priorities or may be difficult to define and implement.** Stakeholders were reminded that no single metric can be everyone's top priority. From a research perspective, some domains from the **FIGURE** will be difficult to define in the short term but can be refined over time as other measures are reported.
4. **Manageable number of metrics.** Performance measurement is burdensome to systems that must collect the data, especially if measures are not aligned with data that are routinely collected or that interfere with work flows. Large numbers of performance measures can quickly overload systems and may reduce participation and the likelihood of meaningful change related to anyone. This can be discouraging and reduce cooperation with future performance measurement efforts.
5. **Third-party facilitation.** HICOR positions itself as a neutral third party that serves all stakeholder groups; thus, the fact that the organization is affiliated with a cancer care delivery system could be seen as problematic by competitors and health insurers. We address this issue with transparency of our methods. There is probably no solution that is completely free of all bias and conflicts of interest.

FIGURE. Results of the Stakeholder Prioritization Processs



Results of the final prioritization exercise at the Value in Cancer Care Summit. Through an iterative voting process initiated with nearly 750 metrics, participants ranked metrics on 2 dimensions: meaningfulness and actionability. The 12 finalists and 6 metrics ultimately endorsed by all stakeholders are listed.

NEXT STEPS

The metric development process within HICOR's Value in Cancer Care Initiative is the first step in a larger vision of designing, implementing, and evaluating approaches to improve cancer care. Like the process of identifying the metrics themselves, we believe the interventions aimed at improving performance should be developed through the multistakeholder engagement process, supported by experts in cancer care delivery, and conducted as prospective, controlled studies. We describe these elements and our plans below.

Creating Value Metrics

Using commercial and public health insurance enrollment and claims records linked to the region's Surveillance, Epidemiology, and End-Results cancer registry, HICOR is quantifying metrics in 4 of the 6 domains shown in the **TABLE**. The active participation of the health insurance community has facilitated timely transfer of insurance records, making the available metrics as close to "real time" as possible. Based on input from the clinical community, metrics are available at the clinic level (vs the provider level). Metric development is an iterative scientific approach that requires the engagement and expertise of clinical, statistical, and scientific programming professionals. The process of creating and reporting metrics requires careful thought, since difficulties with numeracy have been shown to be a barrier to understanding data for laypersons and even professionals.[13-18] A regional, stakeholder-based approach allows the opportunity for individual participation and feedback to the approach as it unfolds, and for one-on-one interaction and modification when necessary to improve the face validity of the metrics.

Reporting the Results

Initially, HICOR is reporting the methods and results privately to the clinics, to ensure that data quality and accuracy issues can be resolved before public reporting of clinic-level records. However, HICOR is dedicated to publicly reporting clinic-specific performance metrics and to providing consumer and patient-facing tools to support decision making such as providing estimates of out-of-pocket costs for treatments with equivalent outcomes.

Optimal display of the information is critical to the overall process. Displaying complex data to a diverse audience has necessitated the engagement of experts in data visualization and user-centered design. For example, providers may wish to monitor their adherence to performance metrics regularly so that clinics can evaluate their progress toward prespecified goals. Patients, on the other hand, may use performance measurement as a way of selecting providers, or as an opportunity for patient-provider interaction regarding particular aspects of care (eg, tumor marker testing following treatment of local-stage breast cancer). To address these issues, HICOR is developing a Web-enabled tool to display reports generated from the linked database noted above. This tool, aimed at providing regional partners with updated reporting on trends in oncology, is now in the beta

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TABLE. Metrics Developed in Top 6 Domains

Biomarker and Molecular Testing
Not yet developed.
Adherence to Primary Therapy Guidelines and Appropriate Use of Targeted Therapies
Advanced imaging for breast staging: use of positron emission tomography, positron emission tomography–computed tomography, computed tomography, or bone scans, 2 months prior to and 2 months following diagnosis.
Testing for breast cancer during surveillance: use of positron emission tomography, computed tomography, bone scans, or tumor markers (CEA, CA 15-3, CA 27.29) during surveillance.
Colony-stimulating factor for first line of chemotherapy: use of colony-stimulating factor within 21 days of the start of low- or intermediate-risk first-line chemotherapy.
Advanced imaging for prostate staging: use of positron emission tomography, positron emission tomography–computed tomography, computed tomography, or bone scans 2 months prior to and 2 months following diagnosis.
Use of Navigator, Care Coordinator, and Case Manager
Not yet developed.
Readmittance and Rate of Avoidable Emergency Department Visits
Hospitalizations during chemotherapy and radiation: inpatient admissions and emergency department (ED) visits in treatment cycle.
Hospitalizations following surgery: inpatient admissions and ED visits in the 90 days following surgery.
Documentation of Consult and Conversation About Palliative Care or Hospice
Hospice at end of life: hospice use in the 30 days prior to death.
Hospitalizations at end-of-life: inpatient or ED hospitalization in the 30 days prior to death.
Imaging at end of life: use of positron emission tomography, positron emission tomography–computed tomography, computed tomography, magnetic resonance imaging, or bone scans in the 30 days prior to death.
Place of death: place of death based on utilization of hospital, hospice, nursing home, or other (including home).
Rate of Chemotherapy in the Last 14 Days of Life
Chemotherapy and radiation at end of life: use of radiation or chemotherapy in the 30 days prior to death.

testing phase with partners. The ultimate goal: to provide results on an interactive website accessible to patients, providers, health insurers, and the purchaser community.

Using the Metric Infrastructure as a Platform for Research-Driven Approaches to Improve Care and Reduce Costs

Performance measurement can be used for Continuous Quality Improvement (CQI) programs, with an emphasis on observational methods and pre- and post evaluations. Our model of stakeholder engagement and regularly updated data linkage provides an opportunity for more formal research designs such as prospective, controlled trials and evaluation of interventions designed to improve quality and reduce costs. When feasible, our goal is to conduct randomized controlled experiments, implemented in the practice setting, and monitored using existing data systems that are already part of standard work flows (eg, insurance claims and electronic medical records)—previously referred to as pragmatic trials.[19] We believe participation of regional stakeholder groups in the design of the intervention and actual conduct of the trial is key to this process. Input from clinical oncology researchers and experts in trial design will support the development of interventions that can be tested in randomized trials and formally evaluated.

Robustness of the Model to a Wide Variety of Interventions

Many different interventions may be effective in improving oncology care where value or performance fails to meet expected targets. Examples range from novel payment models (eg, pay-for-performance methods) to delivery system changes (eg, automated order entry systems) to tools for patient or provider behavior change (eg, interactive videos, shared decision-making tools). Our network provides us with the opportunity to test and monitor the impact of a wide range of interventions in clinical practice settings, and then to scale up those interventions that appear promising for formal testing via controlled studies. Interventions that do not show improvement can be quickly shelved. Such rapid evaluation and redirection of effort can be difficult and cumbersome in the traditional CQI model.

THE POTENTIAL IMPACT OF OUR APPROACH

The Value in Cancer Care Consortium is the first step toward linking national quality and value efforts with real-world clinical practice and patient experience in a local region. We can rapidly develop and evaluate practical, applied models for translating policy to practice in a grassroots or real-world setting. While healthcare policies are often developed nationally, the implementation of those policies and their impact on patients, providers, and payers is most evident at the local or regional level, potentially allowing more rapid adaptation or intervention. Our strategy provides a real-world laboratory for developing and accessing promising interventions to improve care. Those that are successful can then be scaled and evaluated elsewhere, such as within integrated regional delivery systems, in clinical trial research networks, or through federal programs such as CMS/Center for Medicare and Medicaid Innovation programs.

SUMMARY

The cost of cancer care continues to increase at an unsustainable rate, and the quality of cancer care delivery has been found to vary considerably. The need for efforts to improve the value of cancer care by improving outcomes while controlling or reducing costs has never been more apparent. In partnership with multiple committed stakeholders—patient groups, health plans, and providers—HICOR is generating consensus-based, clinically relevant, and actionable performance measures. These measures can be employed to:

- Design and evaluate practice changes in healthcare delivery
- Monitor the impact of the changes at the clinic, provider, and patient levels
- Develop new interventions, including performance improvement programs, as well as actual experiments, rapidly and efficiently

This multistakeholder regional partnership is providing a real-world platform for the development and evaluation of promising interventions to improve the quality and value of cancer care in the 21st century, both regionally and nationally. **EBO**

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Q&A on Palliative Care

Andrew Smith

ABOUT THE EXPERT

RANDALL KARKAUER, MD

Randall Krakauer, MD, vice president and national medical director for Medical Strategy at Aetna, who helped design Aetna's Compassionate Care Program (ACCP) that was launched in 2004, says that its consistent success illustrates why palliative care should become the standard of care for many of the sickest patients.

"Improving the quality of care for those with advanced illness represents a tremendous opportunity for the country's health system, and particularly for Medicare, for individual patients, and for families and caregivers."

—RANDALL KARKAUER, MD

Randall Krakauer, MD, vice president and national medical director for Medical Strategy at Aetna, who helped design Aetna's Compassionate Care Program (ACCP) that was launched in 2004, says that its consistent success illustrates why palliative care should become the standard of care for many of the sickest patients.

Q: WHO IS ELIGIBLE FOR THE PROGRAM?

A: ACCP focuses on patients with advanced illness, which refers to a medical condition that has progressed to the point that therapy designed to substantially reverse the pathological process is no longer effective or appropriate. Almost 50% of participants in ACCP have cancer. Others have a variety of conditions including heart disease, kidney disease, lung disease, and, most frequently, a combination of conditions. For these patients, decision support, psychosocial support, pain relief, palliative care, and related services are the most appropriate approach.

Q: HOW MANY AETNA MEMBERS USE THE PROGRAM AT ANY GIVEN TIME?

A: We are engaging a little less than 1% of the 600,000 people in our Medicare population, and we also provide the service for our commercially insured population. The percentage of people with advanced illness in our commercial population is much smaller than it is in the Medicare population. Still, given the overall size of the population, we serve several hundred commercial patients a year.

Q: HOW DOES THE PROGRAM WORK?

A: We identify eligible members with advanced illness through various means, including an algorithm that analyzes claims and transactions, self-referrals, and physician referrals.

We reach out to these members and offer advice, assistance, and support from case managers. Most of the case managers are nurses, though some are social workers. They receive special training and mentoring in advanced illness and palliative care issues and frequently help members and their families address concerns that may be difficult to face. Most of them have considerable experience. They connect not only with individual patients but also with their physicians, families, caregivers, and others. They provide decision support on care options including hospice. They provide psychosocial support. They facilitate pain relief. They provide links to social service agencies where necessary or appropriate.

Q: WHEN DID AETNA LAUNCH THE PROGRAM?

A: ACCP was launched almost 10 years ago, after we had built a robust case management capability for our Medicare population. We identified advanced illness as an area where these case managers could add significant support and value. We recognized that the default choices for treatment and end-of-life care in the healthcare system did not reasonably represent informed decision-making—patients who got the appropriate information and assistance would often make other decisions.

Q: HOW BIG AN IMPACT HAS THE PROGRAM HAD ON PATIENTS?

A: Every metric we monitor indicates extraordinarily favorable impact in health outcomes and satisfaction. My favorite illustration of this is the remarkable fact that we have run this program for nearly a decade and we have not received a single member complaint.

On the health outcomes side, the program dramatically changes how our members use medical services. Among our engaged Medicare population, there has been an 82% reduction in acute hospital days, an 86% reduction in intensive care days, and an 82% hospice election rate. As a result, more than $12,500 in medical costs is avoided for every member engaged in this program. Most importantly, member satisfaction increases as well.

Q: HOW DO YOU ADVERTISE THE EXISTENCE OF THE PROGRAM TO PATIENTS?

A: Most of the members are identified through claims data or our care management processes. We have described this program in a newsletter that went to all of our Medicare Advantage members and had stories in national publications such as *The Wall Street Journal*. We have put considerably more effort, however, into outreach aimed at physicians. We have sent nurses to visit physician offices, describe this program, solicit referrals, and work with physicians in collaborative arrangements with us. The number of physician referrals is increasing, but there is still opportunity for more referral growth.

Q: HOW DO CASE MANAGERS CHOOSE WHICH PROVIDERS TO USE WHEN PATIENTS NEED SERVICES?

A: Most large hospitals now have palliative care physicians or services, so in-patient palliative care is easier to find than it used to be. There is still a significant shortage of outpatient palliative care, though, so we strive to find ways to provide home care services. We work with many hospices, some of which also provide outpatient palliative care. We build relationships with those hospices and with other service providers and aging associations in markets where we have members.

Q: HOW WOULD YOU LIKE TO EXPAND OR IMPROVE THE PROGRAM GOING FORWARD?

A: We would like to identify far more eligible patients than we currently do and identify them earlier. Aetna's Medicare membership experiences a 4.5% average annual mortality rate. Improving the quality of care for those with advanced illness represents a tremendous opportunity for the country's health system, and particularly for Medicare, for individual patients, and for families and caregivers.

To help remove a barrier in accessing hospice care, Aetna has eliminated the requirement that commercial members give up "curative" treatment to be eligible for hospice benefits.

In addition, we have taken a more liberal approach to defining hospice eligibility so that members may receive access to hospice care earlier. Commercial-insured members with a terminal diagnosis of 12 months are eligible for hospice care, as opposed to the previous standard of 6 months. We have not seen evidence of increased cost as a result of this.

We would like to make the same changes for our Medicare population, and continue to seek approval from Medicare to do this. **EBO**

The Challenges With Ensuring the Validity and Utility of Diagnostic Tests

Surabhi Dangi-Garimella, PhD

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Precision medicine has touched every aspect of healthcare today, and—as is evident from President Obama's State of the Union speech for 2015—is front of mind with the federal government, which has plans to increase basic research funding for the National Institutes of Health and boost the regulatory role of the FDA. However, while diagnostic tests play a critical role in physician decision making—particularly in oncology—by generating data to improve treatment outcomes, questions remain regarding the clinical utility of some of these tests, as well as the validity of laboratory-developed tests (LDTs). While next-generation sequencing is on the horizon for the FDA's regulatory purview, assessing the validity and utility of existing FDA-approved tests and LDTs, and deciding who pays for the tests, are important issues that remain unaddressed.

The American Journal of Managed Care convened an expert panel of 2 payer representatives and 2 practicing oncologists that I moderated, to discuss these and other issues with diagnostic testing that are plaguing the healthcare world. Unique perspectives on the topic were contributed by Francisco J. Esteva, MD, PhD, professor of medicine, director of breast medical oncology, and associate director of clinical investigation, Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center; Daniel F. Hayes, MD, clinical director, Breast Oncology Program, Stuart B. Padnos professor in breast cancer research, University of Michigan Comprehensive Cancer Center; John L. Fox, MD, MHA, associate vice president, medical affairs, Priority Health; and Bryan Loy, MD, MBA, vice president oncology, laboratory and personalized medicine, Humana.

The discussion started with the panelists being asked to scrutinize the "value" of a diagnostic test beyond its analytical performance: "Between outcomes for a particular patient population, improved healthcare quality, the cost of a test, and how complex the procedure is for conducting a particular test, what are the different parameters that clinicians and payers consider?"

For a long time, biomarkers included in these diagnostic tests had not been validated, answered Esteva, resulting in smaller retrospective—not prospective—trials being conducted to evaluate the tests. Referring to biomarkers identified in breast cancer, he added that the estrogen receptor (ER), the progesterone receptor, and HER2—the standard of care—had not been validated via a prospective trial. While he believes that despite the lack of prospective data, there is value of some of the new diagnostic tests used in breast cancer, such as OncotypeDx, Mammaprint, and Prosigna, he sees a problem with the lack of clinical or outcomes data of some of the genomic/next-generation sequencing tests now in use.

According to Hayes, we critically need to take 3 actions: modify the regulatory environment, discuss the analytical validity of a diagnostic test, and identify who really decides the utility of LDTs. Unlike drug manufacturers, whose products face rigorous evaluation through clinical trials, manufacturers of diagnostic tests have the option of gaining FDA approval through a Premarket Approval process, or 510(k) clearance, or an FDA-independent process that requires approval through the CMS-initiated Clinical and Laboratory Improvement Amendments (CLIAs). LDTs, developed by individual laboratories, can escape FDA evaluation as long as they have CLIA approval, which "really means that the laboratory adheres to good laboratory practices, but has nothing to do with the value of that test to take care of an individual patient," he emphasized.

> *"We critically need to take 3 actions: modify the regulatory environment, discuss the analytical validity of a diagnostic test, and identify who really decides the utility of LDTs."*
>
> —DANIEL F. HAYES, MD

The "clinical utility" of a diagnostic test needs attention, said Hayes, because it indicates whether analyzing for the particular biomarker on the diagnostic test improves patient outcomes. However, he pointed out that the FDA approval process does not require the manufacturer to establish clinical utility—analytical and clinical validity suffice. So the FDA-approved tests, in his opinion, may not be valuable in terms of patient care, and even if they are, there are no studies to prove so. While acknowledging that some of the LDTs in use are quite good, he pointed to the fact that this has led to a "buyer beware" market. However, he added, there is a need to clarify who should be the most vigilant—patient, doctor, third-party payers, or practice guidelines committees like the American Society of Clinical Oncology (ASCO) or the National Comprehensive Cancer Network (NCCN).

Fox said that he distinguishes predictive tests from prognostic tests. In his opinion, while the clinical utility of predictive tests is on the right track, he identifies problems with the clinical utility of prognostic tests. Even though a good association between the prognostic test and an outcome may be established, he said, informed decisions are lacking.

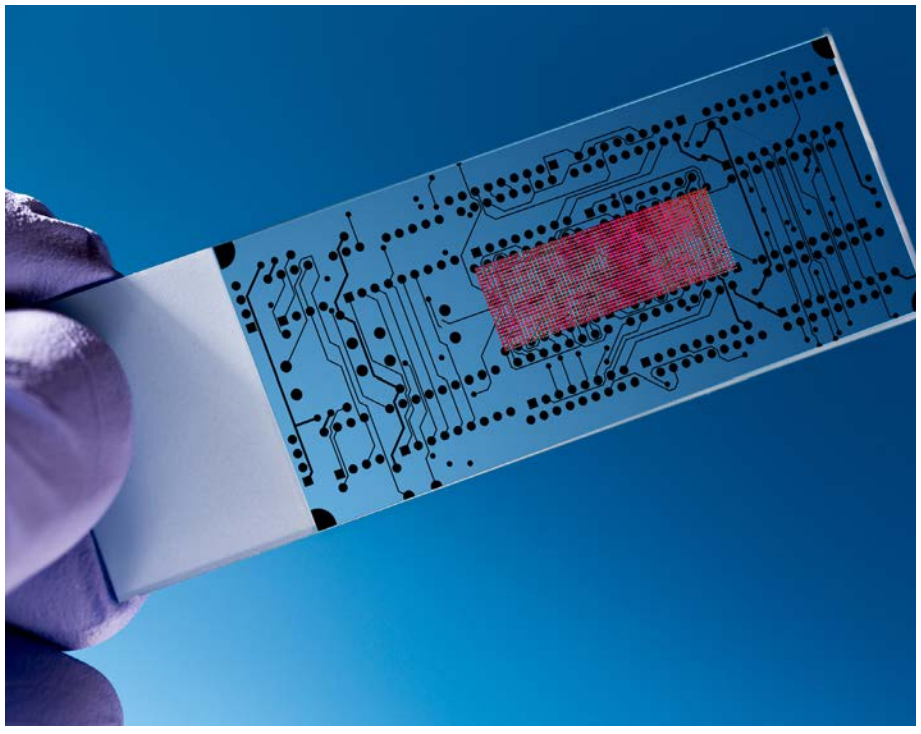
Loy agreed with Fox that a perfectly good test yields no value for payers if used inappropriately. Pointing to deficiencies in the process—between the test being ordered by an oncologist and the results being produced—he said that as a payer, "The whole system of care is very important to us." While reiterating that CLIA approval is contingent only on good laboratory practices, Loy added that in addition to the test performance, the results and how they are presented to the clinicians for interpretation are drawing payers' attention, along with the incremental utility of a test to ensure coverage.

Fox alluded to the FDA announcement that LDTs, especially those used for high-risk prediction and to guide treatment, will need pre-market review by the FDA.[1] He worries that this will restrict the development of the tests and may not necessarily solve the problem. Hayes argued that several laboratories are developing these indigenous diagnostic tests without demonstrating any analytical validity or clinical validity, which would never be allowed if they were developing a therapeutic regimen. Applauding the FDA decision, Hayes said it will greatly improve the field. He believes that rather than suppress innovation, a well-developed test that bears the promise of getting the right drug to the right patient may in fact garner the

support of third-party payers.

Citing a workshop on the topic that he helped develop, Hayes pointed to 2 possible ways of generating valuable evidence with these tests: 1) conduct a prospective clinical trial; or 2) conduct a retrospective trial with archived tumor specimens from previous clinical trials, but only after drafting a complete protocol that would include the laboratory, statistical, and analytical plan—a "prospective retrospective study."

While agreeing with Hayes, Loy said that such efforts are already being considered and that increased governance by the FDA will help payers improve their understanding of the clinical utility of a test by ensuring accountability. Citing the examples of HER2 and ER that Esteva referred to, he added that we are still learning about these tests because much needed information was not available earlier. Hayes added that the CancerLinQ program being developed by ASCO, which is expected to be launched later this year in partnership with the software company SAP,[2,3] would be a big help. "I think one of the hopes of ASCO is that CancerLinQ will at least provide relatively consistent guidelines across the country," he said, adding that while it will not replace clinical judgment, it will provide data on how tests and drugs work in the real world.



THE ROLE OF NCCN AND ASCO

Acknowledging that the NCCN and ASCO greatly influence the use of pharmaceutical drugs and biologicals, Esteva pointed out that the lack of evidence with diagnostic tests might result in initial guidelines being developed by the organizations based on expert opinions alone. However, he thinks the NCCN, ASCO, and the European Society for Medical Oncology will lead the guideline-development front for test developers. While NCCN guidelines direct a clinical pathway approach, ASCO, Hayes said, looks at evidence-based personalization of the treatment; the 2 together work well toward standardizing clinical practice, he added.

> *"From a payer's viewpoint, there is value in paying for genetic testing that can help personalize treatment and direct appropriate use of drugs like Tarceva and Herceptin, avoiding false-positive treatment."*
>
> —JOHN L. FOX, MD, MHA

Fox said that from a payer's viewpoint, there is value in paying for genetic testing that can help personalize treatment and direct appropriate use of drugs like Tarceva and Herceptin, avoiding false-positive treatment. As a payer, he thinks that these tests are underutilized, as patients who should be tested are not and may not receive the most appropriate therapy. Hayes responded that he was happy to hear of the change in approach by the payer community, citing an experience he had a few years earlier when presenting a case for the OncotypeDx test that was still under development. Hayes related how when he presented data on the value of the 21-gene panel test to Blue Cross and Blue Shield—it could help identify ER-positive, node-negative patients who would not benefit from chemotherapy—the company representative said that while such an expensive test might be ordered by oncologists, they would continue chemotherapy in spite of its results. "If we put our money where our mouth is, if we're going to use these tests, if we're going to order these tests, we need to use the tests to drive care, but that means we've got to be sure that the tests are accurate and reliable."

Esteva thinks that while the NCCN and ASCO provide valuable guidelines, the organizations need to keep up their pace in including tests that have been FDA approved or have updated validity or utility data, to avoid barriers to the use of the approved tests. Fox agreed, adding that Priority Health is ready to pay for drugs and tests included in the NCCN guidelines, but if a valuable test is not included in the guideline, it poses a challenge.

GENETIC COUNSELORS

Loy stressed the importance of the role of genetic counselors in the process, indicating that Humana has them on board. He said that sometimes those who order the tests may not be sufficiently informed and may order the wrong test or misinterpret the results, which can affect treatment decisions. He also highlighted the importance of involving patients in the conversation and keeping them informed.

In Esteva's opinion, while genetic counselors can prove valuable in discussions on determining a patient's risk for developing cancer, he thinks they may have limited input with treatment decisions. Hayes agreed, and added that getting the different providers taking care of the patient to work as a team can eliminate discrepancies in who orders the tests and what treatment ensues.

In Loy's opinion, too, the end user—the medical oncologist who drives treatment—should be the decision maker regarding which diagnostic test should be ordered, but added that he's concerned with the lack of consideration for medical history prior to ordering tests for [breast cancer markers] *BRCA1* and *BRCA2*. "It feels like we still have a long way to go in terms of creating some accountability and a measurement and education system to be able to get folks ordering (tests) thoughtfully and getting the results—getting the most value out of the dollars that will be spent on the tests, both in screening but to a lesser extent in the predictive and the prognostic arena." Reemphasizing the need for educated decisions in diagnostic testing, Fox added that Priority requires genetic counselors be involved before patients are tested and also to discuss results after.

According to Hayes, diagnostic tests have immense value in deciding who not to treat. It is known, he said, that ER-negative patients do not benefit from anti-estrogen therapy. "We're willing to withhold a pretty tolerable drug that, if it works, has enormous benefit, but we're still willing to withhold it from that group of patients." On the flip side, he said that ordering panels of tests to screen for the risk of susceptibility to various cancers is uncalled for.

Fox and Hayes then discussed how this process could be streamlined so patients are appropriately tested at the point of care and whether ASCO could be involved in the process, which brought the discussion back to CancerLinQ and how it could strengthen clinical decision support.

The discussion ended with the participants reiterating the importance of multi-stakeholder involvement in the process, additional regulation and better guidelines, accountability, and systems that could integrate clinical information with molecular data—all of which would contribute to achieving improved clinical decisions at lower costs. **EBO**

To hear the complete discussion, visit http://bit.ly/16tLVmr.

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Medical World News®

MANAGED CARE UPDATES

Study Suggests Lung Cancer Screening Criteria May Not Capture All Smokers Who Need It

Mary K. Caffrey

CMS gained attention in February when officials announced Medicare would cover lung cancer screening for high-risk individuals meeting certain criteria, which were largely spelled out by the US Preventive Services Task Force (USPSTF).[1]

However, a study published shortly afterward in the *Journal of the American Medical Association* (*JAMA*) suggests the criteria may exclude many potential lung cancer patients who would benefit from screening.[2] Ironically, based on the data uncovered by the *JAMA* study, efforts to get long-term smokers to quit in recent decades makes some of them ineligible for screening with low-dose computed tomography (LDCT), because they have not smoked for more than 15 years.

The study, by Ping Yang, MD, PhD, and colleagues at the Mayo Clinic in Rochester, Minnesota, evaluated trends in the proportion of patients with lung cancer meeting the USPSTF criteria. Researchers looked at 140,000 residents in Olmstead County, Minnesota, who were 20 years or older, between 1984 and 2011. All confirmed cases of lung cancer were identified using the Rochester Epidemiology Project database, adjusting for age and gender distribution in the US population in 2000. The proportion of cases meeting USPSTF criteria were identified. Those eligible were asymptomatic adults 55 to 80 years of age who had a 30 pack-year smoking history. This means the person smoked the equivalent of a pack a day for 30 years; a person could also have smoked 2 packs a day for 15 years. To be screened, a person had to be a current smoker or have quit within the past 15 years. (Medicare eligibility criteria are similar; the cutoff for LDCT coverage is 77 years.[3])

Researchers identified 1351 patients with a new diagnosis of primary lung cancer between 1984 and 2011. However, the proportion of patients with lung cancer who smoked more than 30 pack-years declined, and proportion of former smokers, especially those who quit more than 15 years ago, increased. Of note, the share of lung cancer patients meeting the USPSTF criteria declined over time, with 57% of patients eligible for screening from 1984 to 1990 and only 43% eligible from 2005 to 2011. The drop-off in eligibility was greater among women—from 52% to 37%; for men the drop-off was 60% to 50%.

"Our findings may reflect a temporal change in smoking patterns in which the proportion of adults with a 30 pack-year smoking history and having quit within 15 years declined," the authors wrote. "The decline in the proportion of patients meeting USPSTF high-risk criteria indicates that an increasing number of patients with lung cancer would not have been candidates for screening. More sensitive screening

criteria may need to be identified while balancing the potential harm from computed tomography."

CMS' decision to screen current and former smokers for lung cancer was based on the results of the National Lung Screening Trial Protocol, which found that patients who received screening had a 15% to 20% lower risk of dying from lung cancer. Results published in 2013 showed that targeting screening toward those at greatest risk produced the most effective results.[4]

However, the decision to pay for widespread screening is not without controversy. In a paper published in *JAMA Internal Medicine* in December 2014, authors Woolf et al expressly discouraged CMS from paying for screening.[5] This is difficult to do under the Affordable Care Act, since the law requires commercial insurers to pay for tests that receive a B recommendation or better from the USPSTF. The authors argued, however, that screening in the general population may not be limited to high-risk smokers outside the clinical trial and may cause unnecessary harm due to radiation and false positives.

Lung cancer is the leading cause of cancer death in the United States; according to the CDC, 156,953 people in the United States died from lung cancer in 2011. The vast majority of deaths from lung cancer are caused by tobacco use.[6] **EBO**

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- Outcomes from Mandatory Genetic Testing and Counseling Programs
- ***Panel:*** The Impact of FDA Regulation on Diagnostics in Oncology

Session 2: Genomics in Oncology, Part 2 - Precision Medicine

- How the President's Precision Medicine Initiative Will Learn From Oncology Practice
- The Patient Lens on Precision Medicine
- ***Panel:*** Reimbursement Challenges for Oncology Innovations: Who Pays?

Session 3: The Future of Immuno-oncology

- Are We Close to the Big "C": Cure?
- Evaluation of Options and Outcomes in a "Me Too" Market
- ***Panel:*** The Role of PBMs in Managing High-Cost Treatment Options

Session 4: Innovations for Patient-Centered Care

- Updates in Big Data for Oncology: What Are We Learning?
- Payment Models in Oncology Care at the Patient Level
- ***Panel:*** Navigating the Conflict of Personalized Medicine vs Population Management

Session 5: Accountable Care in Oncology

- ***Panel:*** Evolution of the ACO Model to Meet the Needs of Oncology Patients and Payers

THE AMERICAN JOURNAL OF MANAGED CARE®

**subject to change*

NEW FDA APPROVAL

CYRAMZA® (ramucirumab), in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

ADVANCING THE SECOND-LINE TREATMENT OF METASTATIC NSCLC[1]

CYRAMZA is the first antiangiogenic agent FDA approved in combination with docetaxel for the second-line treatment of metastatic NSCLC, including nonsquamous and squamous histologies.[1]

CYRAMZA™
ramucirumab injection
10 mg/mL solution

TAKE ACTION

IMPORTANT SAFETY INFORMATION FOR CYRAMZA

WARNING: HEMORRHAGE
CYRAMZA increased the risk of hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Warnings and Precautions

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage including severe and sometimes fatal hemorrhagic events. In Study 3, which evaluated CYRAMZA plus docetaxel in metastatic non-small cell lung cancer (NSCLC), the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDs or other antiplatelet therapy other than once-daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from Study 3; therefore, the risk of pulmonary hemorrhage in these groups of patients is unknown. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events

- Serious, sometimes fatal, arterial thromboembolic events (ATEs) including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials including 1.7% of 236 patients who received CYRAMZA as a single agent for gastric cancer in Study 1. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA plus docetaxel (6%) as compared to placebo plus docetaxel (2%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, infusion-related reactions (IRRs) occurred in 6 out of 37 patients (16%), including 2 severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for Grade 3 or 4 IRRs.

Gastrointestinal Perforations

- CYRAMZA is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. In Study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel versus 0.3% for placebo plus docetaxel. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- CYRAMZA has not been studied in patients with serious or nonhealing wounds. CYRAMZA is an antiangiogenic therapy with the potential to adversely affect wound healing. Withhold CYRAMZA prior to surgery. Resume CYRAMZA following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.

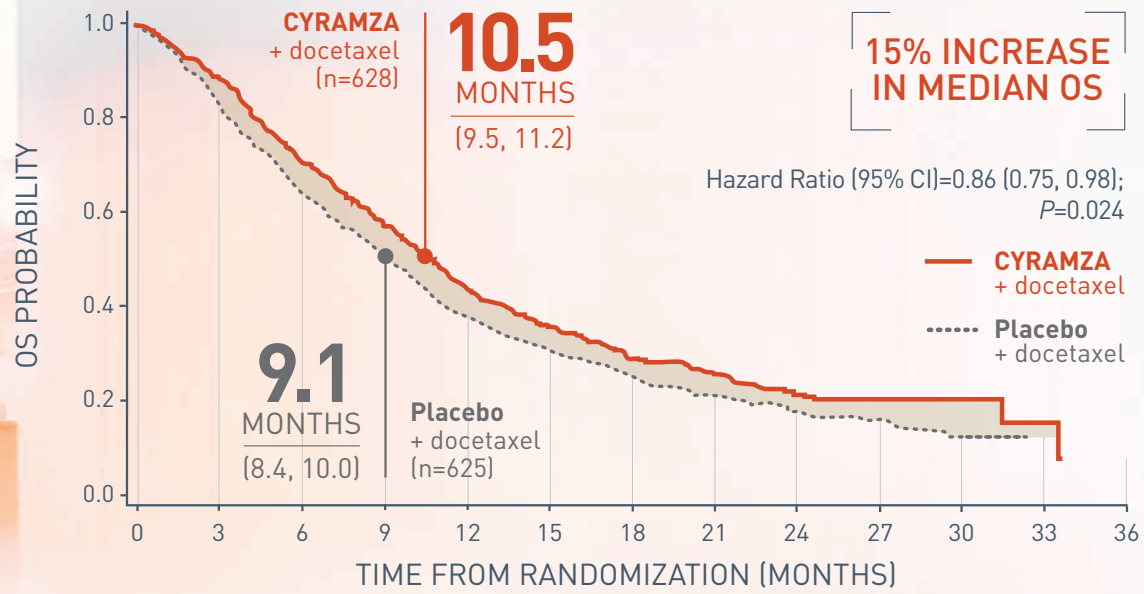
Clinical Deterioration in Child-Pugh B or C Cirrhosis

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

CYRAMZA PLUS DOCETAXEL DEMONSTRATED A STATISTICALLY SIGNIFICANT IMPROVEMENT IN OVERALL SURVIVAL VS DOCETAXEL[1]

OVERALL SURVIVAL: MEDIAN - MONTHS (95% CI)

MAJOR OUTCOME MEASURE



Number at Risk

CYRAMZA + docetaxel	628	527	415	329	231	156	103	70	45	23	11	2	0
Placebo + docetaxel	625	501	386	306	197	129	86	56	36	23	9	0	0

- The percentage of deaths at the time of analysis was 68% (428 patients) and 73% (456 patients) in the CYRAMZA plus docetaxel and placebo plus docetaxel arms, respectively[1]

Demonstrated improvements across all three efficacy outcomes (OS, PFS, ORR)[1]

- **Median PFS** with CYRAMZA plus docetaxel was 4.5 months (95% CI: 4.2, 5.4) vs 3.0 months (95% CI: 2.8, 3.9) with placebo plus docetaxel (hazard ratio 0.76 [95% CI: 0.68, 0.86]; *P*<0.001)
  - The percentage of events at the time of analysis was 89% (558 patients) and 93% (583 patients) in the CYRAMZA plus docetaxel and placebo plus docetaxel arms, respectively
- **ORR** with CYRAMZA plus docetaxel was 23% (95% CI: 20, 26) vs 14% (95% CI: 11, 17) with placebo plus docetaxel (*P*<0.001)*

CI=confidence interval; OS=overall survival; PFS=progression-free survival; ORR=objective response rate.

*ITT population. Disease progression and tumor response were assessed by investigators in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[2] ORR is defined as complete plus partial response.

REVEL TRIAL DESIGN (N=1253)

The phase III REVEL trial evaluated the efficacy and safety of CYRAMZA plus docetaxel vs placebo plus docetaxel in patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Major efficacy outcome measure was OS. Supportive efficacy outcome measures were PFS and ORR. All patients were required to have Eastern Cooperative Oncology Group performance status 0 or 1. Patients were randomized 1:1 (N=1253) to receive either CYRAMZA 10 mg/kg or placebo, in combination with docetaxel at 75 mg/m^2 every 21 days.[1]

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- RPLS has been reported at a rate of <0.1% in clinical studies with CYRAMZA. Confirm the diagnosis of RPLS with MRI and discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

Most Common Adverse Reactions

- The most commonly reported adverse reactions (all grades; Grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus docetaxel and ≥2% higher than placebo plus docetaxel in Study 3 were neutropenia (55% vs 46%; 49% vs 40%), fatigue/asthenia (55% vs 50%; 14% vs 11%), stomatitis/mucosal inflammation (37% vs 19%; 7% vs 2%), epistaxis (19% vs 7%; <1% vs <1%), febrile neutropenia (16% vs 10%; 16% vs 10%), peripheral edema (16% vs 9%; 0% vs <1%), thrombocytopenia (13% vs 5%; 3% vs <1%), lacrimation increased (13% vs 5%; <1% vs 0%), and hypertension (11% vs 5%; 6% vs 2%).
- The most common serious adverse events with CYRAMZA plus docetaxel in Study 3 were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel.
- Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel-treated patients (9%) than in placebo plus docetaxel-treated patients (5%). The most common adverse events leading to treatment discontinuation of CYRAMZA were infusion-related reaction (0.5%) and epistaxis (0.3%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA plus docetaxel-treated patients in Study 3 were hyponatremia (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (3.3% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

Drug Interactions

- No pharmacokinetic interactions were observed between ramucirumab and docetaxel.

Use in Specific Populations

- Pregnancy Category C: Based on its mechanism of action, CYRAMZA may cause fetal harm. Advise females of reproductive potential to avoid getting pregnant, including use of adequate contraception, while receiving CYRAMZA and for at least 3 months after the last dose of CYRAMZA. Animal models link angiogenesis, VEGF and VEGF Receptor 2 to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no adequate or well-controlled studies of ramucirumab in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.
- Nursing Mothers: It is recommended to discontinue nursing or discontinue CYRAMZA due to the potential risks to the nursing infant.
- Females of Reproductive Potential: Advise females of reproductive potential that CYRAMZA may impair fertility.

Please see Brief Summary of Prescribing Information for CYRAMZA, including Boxed Warning for hemorrhage, on the next page.

RB-L HCP ISI 17DEC2014

References: 1. CYRAMZA (ramucirumab) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2014. **2.** Garon EB, Ciuleanu T-E, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384(9944):665-673.

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Lilly

CYRAMZA® (ramucirumab) injection

BRIEF SUMMARY: For complete safety, please consult the full Prescribing Information.

WARNING: HEMORRHAGE
CYRAMZA increased the risk of hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

INDICATIONS AND USAGE

Non-Small Cell Lung Cancer:
CYRAMZA, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Hemorrhage
CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In Study 1, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In Study 2, the incidence of severe bleeding was 4.3% for CYRAMZA plus paclitaxel and 2.4% for placebo plus paclitaxel. Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in Studies 1 and 2; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. In Study 3, the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDS or other anti-platelet therapy other than once daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from Study 3; therefore, the risk of pulmonary hemorrhage in these groups of patients is unknown. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events
Serious, sometimes fatal, arterial thromboembolic events (ATEs) including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials including 1.7% of 236 patients who received CYRAMZA as a single agent for gastric cancer in Study 1. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension
An increased incidence of severe hypertension occurred in patients receiving CYRAMZA as a single agent (8%) as compared to placebo (3%) and in patients receiving CYRAMZA plus paclitaxel (15%) as compared to placebo plus paclitaxel (3%) and in patients receiving CYRAMZA plus docetaxel (6%) as compared to placebo plus docetaxel (2%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions
Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, infusion-related reactions (IRRs) occurred in 6 out of 37 patients (16%), including two severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for Grade 3 or 4 IRRs.

Gastrointestinal Perforations
CYRAMZA is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. Four of 570 patients (0.7%) who received CYRAMZA as a single agent in clinical trials experienced gastrointestinal perforation. In Study 2, the incidence of gastrointestinal perforations was also increased in patients that received CYRAMZA plus paclitaxel (1.2%) as compared to patients receiving placebo plus paclitaxel (0.3%). In Study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel and 0.3% for placebo plus docetaxel. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing
CYRAMZA has not been studied in patients with serious or non-healing wounds. CYRAMZA is an antiangiogenic therapy with the potential to adversely affect wound healing. Withhold CYRAMZA prior to surgery. Resume following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.

Clinical Deterioration in Patients with Child-Pugh B or C Cirrhosis
Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
RPLS has been reported with a rate of <0.1% in clinical studies with CYRAMZA. Confirm the diagnosis of RPLS with MRI and discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

ADVERSE REACTIONS

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

CYRAMZA Administered in Combination with Docetaxel
Study 3 was a multinational, randomized, double-blind study conducted in patients with NSCLC with disease progression on or after one platinum-based therapy for locally advanced or metastatic disease. Patients received either CYRAMZA 10 mg/kg intravenously plus docetaxel 75 mg/m^2 intravenously every 3 weeks or placebo plus docetaxel 75 mg/m^2 intravenously every 3 weeks. Due to an increased incidence of neutropenia and febrile neutropenia in patients enrolled in East Asian sites, Study 3 was amended and 24 patients (11 CYRAMZA plus docetaxel, 13 placebo plus docetaxel) at East Asian sites received a starting dose of docetaxel at 60 mg/m^2 every 3 weeks. Study 3 excluded patients with an ECOG PS of 2 or greater, bilirubin greater than the upper limit of normal (ULN), uncontrolled hypertension, major surgery within 28 days, radiographic evidence of major airway or blood vessel invasion by cancer, radiographic evidence of intra-tumor cavitation, or gross hemoptysis within the preceding 2 months, and patients receiving therapeutic anticoagulation or chronic anti-platelet therapy other than once daily aspirin. The study also excluded patients whose only prior treatment for advanced NSCLC was a tyrosine kinase (epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK]) inhibitor. The data described below reflect exposure to CYRAMZA plus docetaxel in 627 patients in Study 3. Demographics and baseline characteristics were similar between treatment arms. Median age was 62 years; 67% of patients were men; 84% were White and 12% were Asian; 33% had ECOG PS 0; 74% had non-squamous histology and 25% had squamous histology. Patients received a median of 4.5 doses of CYRAMZA; the median duration of exposure was 3.5 months, and 195 (31% of 627) patients received CYRAMZA for at least six months. In Study 3, the most common adverse reactions (all grades) observed in CYRAMZA plus docetaxel-treated patients at a rate of ≥30% and ≥2% higher than placebo plus docetaxel were neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation. Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel-treated patients (9%) than in placebo plus docetaxel-treated patients (5%). The most common adverse events leading to treatment discontinuation of CYRAMZA were infusion-related reaction (0.5%) and epistaxis (0.3%). For patients with non-squamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of ≥Grade 3 pulmonary hemorrhage was 1% for CYRAMZA plus docetaxel compared to 6% overall incidence and 1% for ≥Grade 3 pulmonary hemorrhage for placebo plus docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of ≥Grade 3 pulmonary hemorrhage was 2% for CYRAMZA plus docetaxel compared to 12% overall incidence and 2% for ≥Grade 3 pulmonary hemorrhage for placebo plus docetaxel. The most common serious adverse events with CYRAMZA plus docetaxel were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel. In patients ≥65 years, there were 18 (8%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 9 (4%) deaths for placebo plus docetaxel. In patients <65 years, there were 13 (3%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 26 (6%) deaths for placebo plus docetaxel. Table 4 provides the frequency and severity of adverse reactions in Study 3.

Table 4: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA in Study 3

Adverse Reactions (MedDRA) System Organ Class	CYRAMZA plus docetaxel (N=627)		Placebo plus docetaxel (N=618)	
	All Grades (Frequency %)	Grade 3-4 (Frequency %)	All Grades (Frequency %)	Grade 3-4 (Frequency %)
Blood and Lymphatic System Disorders				
Febrile neutropenia	16	16	10	10
Neutropenia	55	49	46	40
Thrombocytopenia	13	3	5	<1
Gastrointestinal Disorders				
Stomatitis/Mucosal inflammation	37	7	19	2
Eye Disorders				
Lacrimation increased	13	<1	5	0
General Disorders and Administration Site Disorders				
Fatigue/Asthenia	55	14	50	11
Peripheral edema	16	0	9	<1
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	19	<1	7	<1
Vascular Disorders				
Hypertension	11	6	5	2

Clinically relevant adverse drug reactions reported in ≥1% and <5% of the CYRAMZA plus docetaxel-treated patients in Study 3 were hyponatremia (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (3.3% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

Immunogenicity
As with all therapeutic proteins, there is the potential for immunogenicity. In 19 clinical trials, 70/2131 (3.3%) of CYRAMZA-treated patients with post baseline serum samples tested positive for treatment-emergent anti-ramucirumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in 12 of the 70 patients who tested positive for treatment-emergent anti-ramucirumab antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to CYRAMZA with the incidences of antibodies to other products may be misleading.

DRUG INTERACTIONS

No pharmacokinetic (PK) interactions were observed between ramucirumab and docetaxel.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category C
Risk Summary
Based on its mechanism of action, CYRAMZA may cause fetal harm. Animal models link angiogenesis, VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no adequate or well-controlled studies of ramucirumab in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.
Animal Data
No animal studies have been specifically conducted to evaluate the effect of ramucirumab on reproduction and fetal development. In mice, loss of the VEGFR2 gene resulted in embryofetal death and these fetuses lacked organized blood vessels and blood islands in the yolk sac. In other models, VEGFR2 signaling was associated with development and maintenance of endometrial and placental vascular function, successful blastocyst implantation, maternal and feto-placental vascular differentiation, and development during early pregnancy in rodents and non-human primates. Disruption of VEGF signaling has also been associated with developmental anomalies including poor development of the cranial region, forelimbs, forebrain, heart, and blood vessels.

Nursing Mothers
It is not known whether CYRAMZA is excreted in human milk. No studies have been conducted to assess CYRAMZA's impact on milk production or its presence in breast milk. Human IgG is excreted in human milk, but published data suggests that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because many drugs are excreted in human milk and because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
The safety and effectiveness of CYRAMZA in pediatric patients have not been established. In animal studies, effects on epiphyseal growth plates were identified. In cynomolgus monkeys, anatomical pathology revealed adverse effects on the epiphyseal growth plate (thickening and osteochondropathy) at all doses tested (5-50 mg/kg). Ramucirumab exposure at the lowest weekly dose tested in the cynomolgus monkey was 0.2 times the exposure in humans at the recommended dose of ramucirumab as a single agent.

Geriatric Use
Of the 563 CYRAMZA-treated patients in two randomized gastric cancer clinical studies, 36% were 65 and over, while 7% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Of the 1253 patients in Study 3, 455 (36%) were 65 and over and 84 (7%) were 75 and over. Of the 627 patients who received CYRAMZA plus docetaxel in Study 3, 237 (38%) were 65 and over, while 45 (7%) were 75 and over. In an exploratory subgroup analysis of Study 3, the hazard ratio for overall survival in patients less than 65 years old was 0.74 (95% CI: 0.62, 0.87) and in patients 65 years or older was 1.10 (95% CI: 0.89, 1.36).

Renal Impairment
No dose adjustment is recommended for patients with renal impairment based on population PK analysis.

Hepatic Impairment
No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin within upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN or total bilirubin >1.0-1.5 times ULN and any AST)

CYRAMZA® (ramucirumab) injection RB-L HCP BS 17Dec2014

based on population PK analysis. Clinical deterioration was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA.

Females and Males of Reproductive Potential

Fertility

Advise females of reproductive potential that CYRAMZA may impair fertility.

Contraception

Based on its mechanism of action, CYRAMZA may cause fetal harm. Advise females of reproductive potential to avoid getting pregnant while receiving CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

DOSAGE AND ADMINISTRATION

Do not administer CYRAMZA as an intravenous push or bolus.

Recommended Dose and Schedule

The recommended dose of CYRAMZA is 10 mg/kg administered by intravenous infusion over approximately 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion. Continue CYRAMZA until disease progression or unacceptable toxicity

Premedication

Prior to each CYRAMZA infusion, premedicate all patients with an intravenous histamine H_1 antagonist (e.g., diphenhydramine hydrochloride). For patients who have experienced a Grade 1 or 2 infusion reaction, also premedicate with dexamethasone (or equivalent) and acetaminophen prior to each CYRAMZA infusion.

Dose Modifications

Infusion-Related Reactions (IRR)

- Reduce the infusion rate of CYRAMZA by 50% for Grade 1 or 2 IRRs.
- Permanently discontinue CYRAMZA for Grade 3 or 4 IRRs.

Hypertension

- Interrupt CYRAMZA for severe hypertension until controlled with medical management.
- Permanently discontinue CYRAMZA for severe hypertension that cannot be controlled with antihypertensive therapy.

Proteinuria

- Interrupt CYRAMZA for urine protein levels ≥2 g/24 hours. Reinitiate treatment at a reduced dose of 8 mg/kg every 2 weeks once the urine protein level returns to <2 g/24 hours. If the protein level ≥2 g/24 hours reoccurs, interrupt CYRAMZA and reduce the dose to 6 mg/kg every 2 weeks once the urine protein level returns to <2 g/24 hours.
- Permanently discontinue CYRAMZA for urine protein level >3 g/24 hours or in the setting of nephrotic syndrome.

Wound Healing Complications

- Interrupt CYRAMZA prior to scheduled surgery until the wound is fully healed.

Arterial Thromboembolic Events, Gastrointestinal Perforation, or Grade 3 or 4 Bleeding

- Permanently discontinue CYRAMZA.

For toxicities related to docetaxel, refer to the current respective prescribing information.

PATIENT COUNSELING INFORMATION

Advise patients:

- That CYRAMZA can cause severe bleeding. Advise patients to contact their health care provider for bleeding or symptoms of bleeding including lightheadedness.
- Of increased risk of an arterial thromboembolic event.
- To undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if symptoms from hypertension occur including severe headache, lightheadedness, or neurologic symptoms.
- To notify their health care provider for severe diarrhea, vomiting, or severe abdominal pain.
- That CYRAMZA has the potential to impair wound healing. Instruct patients not to undergo surgery without first discussing this potential risk with their health care provider.
- Of the potential risk for maintaining pregnancy, risk to the fetus, or risk to postnatal development during and following treatment with CYRAMZA and the need to avoid getting pregnant, including use of adequate contraception, for at least 3 months following the last dose of CYRAMZA.
- To discontinue nursing during CYRAMZA treatment.

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

Lilly

CYRAMZA® (ramucirumab) injection

RB-L HCP BS 17Dec2014

Medical World News®

MANAGED CARE UPDATES

From *Choosing Wisely*, Advice for Palliative Care Specialists and Guidance for Cancer Patients

Mary K. Caffrey

The *Choosing Wisely* initiative, created by the American Board of Internal Medicine (ABIM) Foundation as a multidisciplinary vehicle to drive discussions about unnecessary tests and costs in medicine, has drawn support from more than 60 different specialties, including the American Society of Clinical Oncology (ASCO).[1]

With its focus on sparing patients from procedures that are duplicative, wasteful, and potentially harmful, *Choosing Wisely* seems a perfect match for the movement toward palliative care. And it has received buy-in from the American Academy of Hospice and Palliative Medicine (AAHPM), which in February 2013 released a list of 5 items that doctors should question before pursuing.

Of greater importance, *Choosing Wisely* produced a consumer document on end-of-life decision making in partnership with ASCO and *Consumer Reports*. Updated in July 2014, this 2-page essay, "Care at the End of Life for Advanced Cancer Patients: When to Stop Cancer Treatment," introduces patients to evidence-based concepts about what is possible in cancer care, the role of a clinical trial, and how palliative can improve quality of life.[2] In clear, consumer-friendly language, the *Choosing Wisely* document speaks to cultural difficulties Americans have discussing end-of-life issues. Last year's Institute of Medicine (IOM) report, *Dying in America*, said these barriers not only prevent patients from receiving palliative care, but also prevent better distribution of healthcare resources in the United States.[3]

"The controversy on this topic and the political desire to avoid it do not alter the fact that every person will face the end of life one day, and many have had hard experience with the final days of a parent, a spouse, a child, a sibling, another relative, or a dear friend," the IOM report states.[3]

The phenomenon is not limited to cancer care. On March 15, 2015, Andrew Ziskind, MD, a cardiologist and healthcare administrator, told a session at the annual meeting of the American College of Cardiology that American cultural attitudes and fear of "death panels" are quite different from prevailing attitudes in Europe. These cultural hurdles have to be overcome, he said, because the pursuit of care at all costs, even when good outcomes are not expected, causes overutilization across the healthcare system.

> *"The controversy on this topic and the political desire to avoid it do not alter the fact that every person will face the end of life one day, and many have had hard experience with the final days of a parent, a spouse, a child, a sibling, another relative, or a dear friend."*
>
> -IOM REPORT

WHAT *CHOOSING WISELY* TELLS PATIENTS

The consumer document tells patients that even with the best cancer care, at some point it may be best to stop. If cancer continues to spread after 3 treatments, the document states, especially in solid tumor cancers such as breast, colon, or lung cancer, physicians have found that "Treatment after treatment offers little or no benefit."[2]

Rather, patients should discuss with their doctor the following:

- What is the real prognosis? How long can I be expected to live with treatment? How long can I be expected to live without treatment?
- What are the goals of treatment? (Patients should discuss whether they are trying to stop the cancer from advancing, or whether they want to ease symptoms.)
- What can I do to improve my quality of life?

While the term "palliative care" ap-

(continued on page **SP189**)

For patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy…

What if You Could Do More?

NOW THERE'S

OPDIVO™ (nivolumab)

Expect More. Do More.

Proven Superior Survival With the Only Immuno-Oncology Therapy in Previously Treated Metastatic Squamous NSCLC

INDICATION

OPDIVO® (nivolumab) is indicated for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

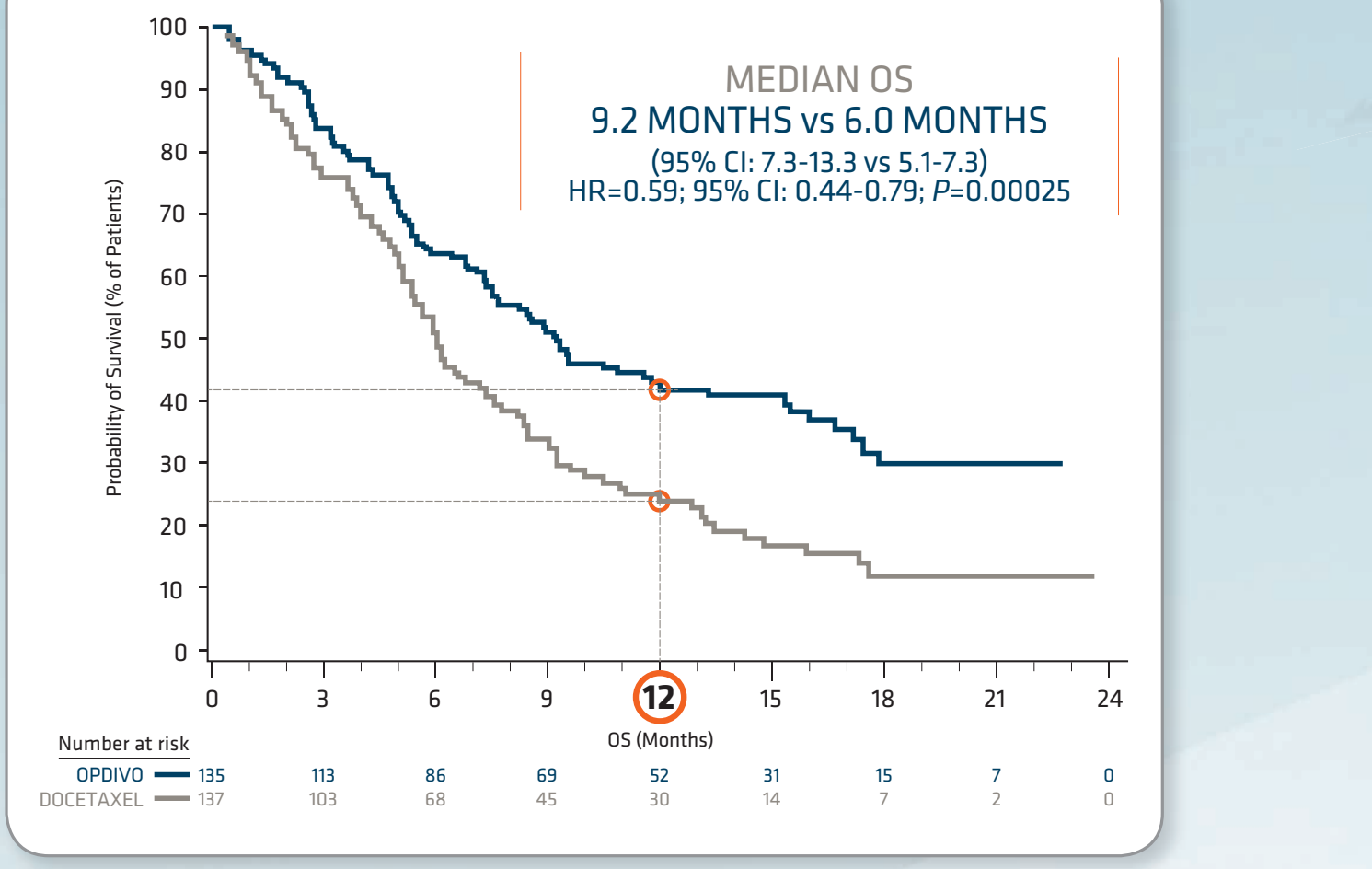
SELECT IMPORTANT SAFETY INFORMATION

OPDIVO is associated with the following Warnings and Precautions including immune-mediated: pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, hypothyroidism, hyperthyroidism, other adverse reactions; and embryofetal toxicity.

Please visit **www.OPDIVO.com/hcp** for more information

For patients with metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy

OPDIVO Demonstrated Superior Survival vs Standard of Care[1-5]



Refer to Figure 1 in the Full Prescribing Information for data on censored patients.
CI=confidence interval; HR=hazard ratio; IV=intravenous; OS=overall survival; PD-1=programmed death-1; PD-L1=programmed death ligand 1.

Study design: OPDIVO was evaluated in a randomized (1:1), open-label, phase 3 study of OPDIVO 3 mg/kg IV every 2 weeks (n=135) vs docetaxel 75 mg/m^2 IV every 3 weeks (n=137). The primary endpoint of the study was overall survival.[1,6]

Results were based on the prespecified interim analysis conducted when 199 events (86% of the planned number of events for final analysis) were observed (86 in the OPDIVO arm and 113 in the docetaxel arm).[1]

- This study included patients regardless of PD-L1 status; PD-L1 testing is not required for a treatment decision

Based on the unprecedented results, OPDIVO achieved the benchmark goal of improving overall survival in metastatic squamous NSCLC

The safety of OPDIVO (3 mg/kg IV over 60 minutes every 2 weeks) was evaluated in CHECKMATE 063 (Trial 3), a single-arm study of 117 patients with metastatic squamous NSCLC who had progressed after receiving a platinum-based therapy and at least one additional systemic treatment regimen.[1,7]

Twenty-nine percent of patients receiving OPDIVO had a drug delay for an adverse reaction.

Serious Adverse Reactions

- In Trial 3, serious adverse reactions occurred in 59% of patients receiving OPDIVO. The most frequent serious adverse drug reactions reported in ≥2% of patients were dyspnea, pneumonia, chronic obstructive pulmonary disease exacerbation, pneumonitis, hypercalcemia, pleural effusion, hemoptysis, and pain.

Common Adverse Reactions

- The most common adverse reactions (≥20%) reported with OPDIVO in Trial 3 were fatigue (50%), dyspnea (38%), musculoskeletal pain (36%), decreased appetite (35%), cough (32%), nausea (29%), and constipation (24%).

Please see additional Important Safety Information on the following page.

Responding to Your Needs in 24 Hours or Less

1-855-OPDIVO-1
(1-855-673-4861)
FOR LIVE SUPPORT AND ASSISTANCE
8:00 AM to 8:00 PM ET, Monday-Friday

Responses provided between 8:00 AM to 8:00 PM ET, Monday-Friday

IMPORTANT SAFETY INFORMATION

Immune-Mediated Pneumonitis

- Severe pneumonitis or interstitial lung disease, including fatal cases, occurred with OPDIVO treatment. Across the clinical trial experience in 691 patients with solid tumors, fatal immune-mediated pneumonitis occurred in 0.7% (5/691) of patients receiving OPDIVO; no cases occurred in Trial 3. In Trial 3, immune-mediated pneumonitis occurred in 6% (7/117) of patients receiving OPDIVO including five Grade 3 and two Grade 2 cases. Monitor patients for signs and symptoms of pneumonitis. Administer corticosteroids for Grade 2 or greater pneumonitis. Permanently discontinue OPDIVO for Grade 3 or 4 and withhold OPDIVO until resolution for Grade 2.

Immune-Mediated Colitis

- In Trial 3, diarrhea occurred in 21% (24/117) of patients receiving OPDIVO. Grade 3 immune-mediated colitis occurred in 0.9% (1/117) of patients. Monitor patients for immune-mediated colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO for Grade 2 or 3. Permanently discontinue OPDIVO for Grade 4 colitis or recurrent colitis upon restarting OPDIVO.

Immune-Mediated Hepatitis

- In Trial 3, the incidences of increased liver test values were AST (16%), alkaline phosphatase (14%), ALT (12%), and total bilirubin (2.7%). Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. Withhold OPDIVO for Grade 2 and permanently discontinue OPDIVO for Grade 3 or 4 immune-mediated hepatitis.

Immune-Mediated Nephritis and Renal Dysfunction

- In Trial 3, the incidence of elevated creatinine was 22%. Immune-mediated renal dysfunction (Grade 2) occurred in 0.9% (1/117) of patients. Monitor patients for elevated serum creatinine prior to and periodically during treatment. For Grade 2 or 3 serum creatinine elevation, withhold OPDIVO and administer corticosteroids; if worsening or no improvement occurs, permanently discontinue OPDIVO. Administer corticosteroids for Grade 4 serum creatinine elevation and permanently discontinue OPDIVO.

Immune-Mediated Hypothyroidism and Hyperthyroidism

- In Trial 3, hypothyroidism occurred in 4.3% (5/117) of patients receiving OPDIVO. Hyperthyroidism occurred in 1.7% (2/117) of patients including one Grade 2 case. Monitor thyroid function prior to and periodically during treatment. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism.

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred in <2% of OPDIVO-treated patients: adrenal insufficiency, uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, autoimmune neuropathy, motor dysfunction and vasculitis. Across clinical trials of OPDIVO administered at doses 3 mg/kg and 10 mg/kg, additional clinically significant, immune-mediated adverse reactions were identified: hypophysitis, diabetic ketoacidosis, hypopituitarism, Guillain-Barré syndrome, and myasthenic syndrome. Based on the severity of adverse reaction, withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy.

Embryofetal Toxicity

- Based on its mechanism of action, OPDIVO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose of OPDIVO.

Lactation

- It is not known whether OPDIVO is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from OPDIVO, advise women to discontinue breastfeeding during treatment.

Serious Adverse Reactions

- In Trial 3, serious adverse reactions occurred in 59% of patients receiving OPDIVO. The most frequent serious adverse drug reactions reported in ≥2% of patients were dyspnea, pneumonia, chronic obstructive pulmonary disease exacerbation, pneumonitis, hypercalcemia, pleural effusion, hemoptysis, and pain.

Common Adverse Reactions

- The most common adverse reactions (≥20%) reported with OPDIVO in Trial 3 were fatigue (50%), dyspnea (38%), musculoskeletal pain (36%), decreased appetite (35%), cough (32%), nausea (29%), and constipation (24%).

Please see brief summary of Full Prescribing Information on the following pages.

References: 1. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2015. **2.** Taxotere [package insert]. Bridgewater, NJ: sanofi-aventis U.S. LLC; 2014. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer V.4.2015. ©2015 National Comprehensive Cancer Network, Inc. All rights reserved. Accessed February 3, 2015. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc. **4.** Garassino MC, Martelli O, Broggini M, et al; on behalf of the TAILOR trialists. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. *Lancet Oncol.* 2013;14(10):981-988. **5.** Kawaguchi T, Ando M, Asami K, et al. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). *J Clin Oncol.* 2014;32(18):1902-1908. **6.** Bristol-Myers Squibb. Study of BMS-936558 (nivolumab) compared to docetaxel in previously treated advanced or metastatic squamous cell non-small cell lung cancer (NSCLC) (CheckMate 017). Identifier: NCT01642004. https://clinicaltrials.gov/ct2/show/NCT01642004. Updated December 31, 2014. Accessed February 5, 2015. **7.** Rizvi NA, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. *Lancet Oncol.* 2015;16:257-265.

OPDIVO™
(nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

Bristol-Myers Squibb

Printed in USA. 1506US15BR00482-02-01 03/15

OPDIVO® (nivolumab) injection, for intravenous use ℞ **ONLY**

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

OPDIVO® (nivolumab) is indicated for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy *[see Clinical Studies (14.2) in full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Immune-Mediated Pneumonitis

Severe pneumonitis or interstitial lung disease, including fatal cases, occurred with OPDIVO treatment. Across the clinical trial experience in 691 patients with solid tumors, fatal immune-mediated pneumonitis occurred in 0.7% (5/691) of patients receiving OPDIVO. No cases of fatal pneumonitis occurred in Trial 3; all five fatal cases occurred in a dose-finding study with OPDIVO doses of 1 mg/kg (two patients), 3 mg/kg (two patients), and 10 mg/kg (one patient).

In Trial 3, pneumonitis occurred in 6% (7/117) of patients receiving OPDIVO, including five Grade 3 and two Grade 2 cases, all immune-mediated. The median time to onset was 3.3 months (range: 1.4 to 13.5 months). All seven patients discontinued OPDIVO for pneumonitis or another event and all seven patients experienced complete resolution of pneumonitis following receipt of high-dose corticosteroids (at least 40 mg prednisone equivalents per day).

Monitor patients for signs and symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater pneumonitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold OPDIVO until resolution for moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.2) in full Prescribing Information]*.

Immune-Mediated Colitis

In Trial 3, diarrhea occurred in 21% (24/117) of patients. Immune-mediated colitis (Grade 3) occurred in 0.9% (1/117) of patients. The time to onset in this patient was 6.7 months. The patient received high-dose corticosteroids and was permanently discontinued from OPDIVO (nivolumab). Complete resolution occurred.

Monitor patients for immune-mediated colitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents. Withhold OPDIVO for Grade 2 or 3 immune-mediated colitis. Permanently discontinue OPDIVO for Grade 4 colitis or for recurrent colitis upon restarting OPDIVO *[see Dosage and Administration (2.2) in full Prescribing Information]*.

Immune-Mediated Hepatitis

In Trial 3, the incidences of increased liver test values were AST (16%), alkaline phosphatase (14%), ALT (12%), and total bilirubin (2.7%). No cases of immune-mediated hepatitis occurred in this trial.

Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater transaminase elevations, with or without concomitant elevation in total bilirubin. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis *[see Dosage and Administration (2.2) in full Prescribing Information and Adverse Reactions]*.

Immune-Mediated Nephritis and Renal Dysfunction

In Trial 3, the incidence of elevated creatinine was 22%. Immune-mediated renal dysfunction (Grade 2) occurred in 0.9% (1/117) of patients. The time to onset in this patient was 0.8 months. The patient received high-dose corticosteroids. OPDIVO was withheld, and the patient discontinued due to disease progression prior to receiving additional OPDIVO. Immune-mediated renal dysfunction was ongoing.

Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) serum creatinine elevation and permanently discontinue OPDIVO. For severe (Grade 3) or moderate (Grade 2) serum creatinine elevation, withhold OPDIVO and administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper; if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue OPDIVO (nivolumab) *[see Dosage and Administration (2.2) in full Prescribing Information and Adverse Reactions]*.

Immune-Mediated Hypothyroidism and Hyperthyroidism

In Trial 3, patients were evaluated for thyroid function at baseline, first day of treatment, and every 6 weeks. Hypothyroidism occurred in 4.3% (5/117) of patients. The median time to onset for these five cases was 4.1 months (range: 1.4 to 4.6 months). All five patients with hypothyroidism received levothyroxine. Complete resolution of hypothyroidism occurred in one patient allowing discontinuation of levothyroxine. Interruption of OPDIVO did not occur in these five patients.

Hyperthyroidism occurred in 1.7% (2/117) of patients. One patient experienced Grade 2 hyperthyroidism 5.2 months after the first dose of OPDIVO, requiring treatment with high-dose corticosteroids and methimazole. Thyroid laboratory tests returned to normal 4.7 months later.

Monitor thyroid function prior to and periodically during treatment. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. There are no recommended dose adjustments of OPDIVO for hypothyroidism or hyperthyroidism.

Other Immune-Mediated Adverse Reactions

Other clinically significant immune-mediated adverse reactions can occur. Immune-mediated adverse reactions may occur after discontinuation of OPDIVO therapy.

The following clinically significant, immune-mediated adverse reactions occurred in less than 2% of OPDIVO-treated patients (n=385): adrenal insufficiency, uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, autoimmune neuropathy, motor dysfunction, and vasculitis.

Across clinical trials of OPDIVO administered at doses of 3 mg/kg and 10 mg/kg the following additional clinically significant, immune-mediated adverse reactions were identified: hypophysitis, diabetic ketoacidosis, hypopituitarism, Guillain-Barré syndrome, and myasthenic syndrome.

For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, withhold OPDIVO, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting OPDIVO after completion of corticosteroid taper based on the severity of the event *[see Dosage and Administration (2.2) in full Prescribing Information]*.

Embryofetal Toxicity

Based on its mechanism of action and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose of OPDIVO *[see Use in Specific Populations]*.

ADVERSE REACTIONS

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

- Immune-Mediated Pneumonitis *[see Warnings and Precautions]*
- Immune-Mediated Colitis *[see Warnings and Precautions]*
- Immune-Mediated Hepatitis *[see Warnings and Precautions]*
- Immune-Mediated Nephritis and Renal Dysfunction *[see Warnings and Precautions]*
- Immune-Mediated Hypothyroidism and Hyperthyroidism *[see Warnings and Precautions]*
- Other Immune-Mediated Adverse Reactions *[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 to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described in the WARNINGS and PRECAUTIONS section and below reflect exposure to OPDIVO in Trial 3, a single-arm trial in patients with metastatic squamous non-small cell lung cancer (NSCLC).

Clinically significant adverse reactions were evaluated in a total of 691 patients enrolled in Trials 1, 3, or an additional dose finding study (n=306) administering OPDIVO (nivolumab) at doses of 0.1 to 10 mg/kg every 2 weeks *[see Warnings and Precautions]*.

Metastatic Squamous Non-Small Cell Lung Cancer

The safety of OPDIVO was evaluated in Trial 3, a single-arm multinational, multicenter trial in 117 patients with metastatic squamous NSCLC and progression on both a prior platinum-based therapy and at least one additional systemic therapy *[see Clinical Studies (14.2) in full Prescribing Information]*. Patients received 3 mg/kg of OPDIVO administered intravenously over 60 minutes every 2 weeks. The median duration of therapy was 2.3 months (range: 1 day to 16.1+ months). Patients received a median of 6 doses (range: 1 to 34).

Trial 3 excluded patients with active autoimmune disease, symptomatic interstitial lung disease, or untreated brain metastasis. The median age of patients was 65 years (range: 37 to 87) with 50% ≥65 years of age and 14% ≥75 years of age. The majority of patients were male (73%) and white (85%). All patients received two or more prior systemic treatments. Baseline disease characteristics of the population were recurrent Stage IIIb (6%), Stage IV (94%), and brain metastases (1.7%). Baseline ECOG performance status was 0 (22%) or 1 (78%).

OPDIVO was discontinued due to adverse reactions in 27% of patients. Twenty-nine percent of patients receiving OPDIVO had a drug delay for an adverse reaction. Serious adverse reactions occurred in 59% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients were dyspnea, pneumonia, chronic obstructive pulmonary disease exacerbation, pneumonitis, hypercalcemia, pleural effusion, hemoptysis, and pain.

Table 1 summarizes adverse reactions that occurred in at least 10% of patients. The most common adverse reactions (reported in at least 20% of patients) were fatigue, dyspnea, musculoskeletal pain, decreased appetite, cough, nausea, and constipation.

Table 1: Adverse Reactions Occurring in ≥10% of Patients for All NCI CTCAE* Grades or ≥5% for Grades 3-4 (Trial 3)

Adverse Reaction	OPDIVO (n=117)	
	All Grades	Grades 3-4
	Percentage (%) of Patients	
General Disorders and Administration Site Conditions		
Fatigue	50	7
Asthenia	19	1.7
Edema[a]	17	1.7
Pyrexia	17	0
Chest pain[b]	13	0
Pain	10	2.6
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	38	9
Cough	32	1.7
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[c]	36	6
Arthralgia[d]	13	0
Metabolism and Nutrition Disorders		
Decreased appetite	35	2.6
Gastrointestinal Disorders		
Nausea	29	1.7
Constipation	24	0
Vomiting	19	0.9
Diarrhea	18	2.6
Abdominal pain[e]	16	1.7
Skin and Subcutaneous Tissue Disorders		
Rash[f]	16	0.9
Pruritus	11	0.9
Investigations		
Decreased weight	13	0.9
Infections and Infestations		
Pneumonia[g]	10	5

(Continued)

Table 1: Adverse Reactions Occurring in ≥10% of Patients for All NCI CTCAE* Grades or ≥5% for Grades 3-4 (Trial 3) *(Continued)*

* National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.
[a] Includes face edema, peripheral edema, local swelling, localized edema, lymphoedema.
[b] Includes chest discomfort and noncardiac chest pain.
[c] Includes back pain, bone pain, musculoskeletal chest pain, myalgia, neck pain, pain in extremity, spinal pain.
[d] Includes arthritis and osteoarthritis.
[e] Includes abdominal pain lower, abdominal pain upper, gastrointestinal pain.
[f] Includes maculopapular rash, rash erythematous, erythema, dermatitis, dermatitis exfoliative, and dermatitis acneiform.
[g] Includes lung infection and pneumonia aspiration.

Other clinically important adverse reactions in less than 10% of patients in Trial 3 were:

General Disorders and Administration Site Conditions: stomatitis

Nervous System Disorders: peripheral neuropathy

Infections and Infestations: bronchitis, upper respiratory tract infection

Table 2: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients for all NCI CTCAE Grades or ≥2% for Grades 3-4 (Trial 3)

Test	Percentage of Patients with Worsening Laboratory Test from Baseline[a]	
	All Grades	Grades 3-4
Chemistry		
Hyponatremia	38	10
Increased creatinine	22	0
Hypercalcemia	20	2.6
Hypokalemia	20	2.6
Hypomagnesemia	20	0
Hypocalcemia	18	1.8
Hyperkalemia	18	4.4
Increased AST	16	0.9
Increased alkaline phosphatase	14	0
Increased ALT	12	0
Hematology		
Lymphopenia	47	16
Anemia	28	2.6
Thrombocytopenia	14	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (range 111 to 114 patients).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

Of 281 patients who were treated with OPDIVO 3 mg/kg every 2 weeks and evaluable for the presence of anti-product antibodies, 24 patients (8.5%) tested positive for treatment-emergent anti-product antibodies by an electrochemiluminescent (ECL) assay. Neutralizing antibodies were detected in two patients (0.7%). There was no evidence of altered pharmacokinetic profile or toxicity profile with anti-product binding antibody development based on the population pharmacokinetic and exposure-response analyses.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample

collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to OPDIVO (nivolumab) with the incidences of antibodies to other products may be misleading.

DRUG INTERACTIONS

No formal pharmacokinetic drug-drug interaction studies have been conducted with OPDIVO.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1) in full Prescribing Information]* and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) in full Prescribing Information].* In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death *[see Data]*. Human IgG4 is known to cross the placental barrier and nivolumab is an immunoglobulin G4 (IgG4); therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. The effects of OPDIVO are likely to be greater during the second and third trimesters of pregnancy. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase fetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis through delivery, at exposure levels of between 9 and 42 times higher than those observed at the clinical dose of 3 mg/kg of nivolumab (based on AUC). Nivolumab administration resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death. Based on its mechanism of action, fetal exposure to nivolumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice. In surviving infants (18 of 32 compared to 11 of 16 vehicle-exposed infants) of cynomolgus monkeys treated with nivolumab, there were no apparent malformations and no effects on neurobehavioral, immunological, or clinical pathology parameters throughout the 6-month postnatal period.

Lactation

Risk Summary

It is not known whether OPDIVO is present in human milk. Because many drugs, including antibodies are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from OPDIVO, advise women to discontinue breastfeeding during treatment with OPDIVO.

Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, OPDIVO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose of OPDIVO.

Pediatric Use

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

Geriatric Use

Clinical studies of OPDIVO did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Of the 117 patients treated with OPDIVO in Trial 3, 50% of patients were 65 years or older and 14% were 75 years or older.

Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended in patients with renal impairment *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended for patients with mild hepatic impairment. OPDIVO (nivolumab) has not been studied in patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

OVERDOSAGE

There is no information on overdosage with OPDIVO.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of OPDIVO, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions]*.
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions]*.
- Hypothyroidism and Hyperthyroidism: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism and hyperthyroidism *[see Warnings and Precautions]*.

Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests *[see Warnings and Precautions]*.

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions, Use in Specific Populations]*.

Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose of OPDIVO *[see Use in Specific Populations]*.

Advise women not to breastfeed while taking OPDIVO *[see Use in Specific Populations]*.

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pears only after halfway down the second page, the document states, "If you decide that you don't want more cancer treatment, then it's time to focus on a kind of palliative care called hospice care." It goes on to describe hospice care as offering help with pain management and symptom relief, grief counseling for family and friends, social worker services, and respite care for caregivers. However, the document does not state that palliative care can start earlier in the cancer treatment process, being designed for patients nearing the end of life.

CHOOSING WISELY FOR PALLIATIVE CARE PROFESSIONALS

An important aspect of *Choosing Wisely* is that the lists of procedures and tests to reconsider are developed within each professional society; the ABIM Foundation initiative distributes the information across medical disciplines, and there is some overlap.

The items that the AAHPM put forward in February 2013 were as follows[4]:

- **Don't recommend percutaneous feeding tubes in patients with advanced dementia; instead, offer oral assisted feeding.** The academy cited studies that found feeding tubes do not improve survival, prevent pneumonia, or heal pressure ulcers—in fact, they have been associated with ulcer development. Assistance with feeding also promotes human interaction, which is as important as nutrition.
- **Don't delay palliative care for a patient** with serious illness who has physical, psychological, social, or spiritual distress because they are pursuing disease-directed treatment. The group cited randomized trials indicating that palliative care improves pain and symptom control and family life, and controls costs.
- **Don't leave an implantable cardioverter-defibrillator (ICD) activated when it is inconsistent with patient and family goals**. The ICD may activate within weeks preceding death, for 25% of patients, causing pain and distress. There are no formal protocols to address deactivation, and fewer than 10% of hospitals have policies. Thus, advance care planning discussions should address this issue.
- **Don't recommend more than a single fraction of palliative radiation for an uncomplicated painful bone metastasis.** Guidelines state that single-fraction radiation to a previously unradiated peripheral bone or vertebral metastasis provides comparable pain relief and morbidity.
- **Don't use topical Ativan, Benadryl, or Haldol (ABH) gel for nausea**. Some topical drugs, such as non-steroidal anti-inflammatory drugs for arthritis symptoms, are safe and effective. Meanwhile, anti-nausea gels have not been proved effective in any large and well-designed trials. **EBO**

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PROVIDER TOOLS

When Is the Right Time for Palliative Care in Oncology?

The Sooner, the Better!

Marian Grant, DNP, CRNP, ACHPN, FPCN

Many professionals in oncology associate palliative care with end-of-life care. While it is true that one type of palliative care, hospice, is for patients in the last months of life, palliative care is much broader than that (see **FIGURE**). In fact, palliative care is appropriate at any age and at any stage in a serious illness like cancer and can be provided *together* with curative treatment. The World Health Organization defines palliative care as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."[1]

FIGURE. Palliative Care Extends Beyond Hospice

The evidence is clear that when patients receive palliative care, their outcomes improve. A 2014 review concluded that palliative care increases patients' quality of life, provides a better overall quality of care with less aggressive end-of-life treatment, and lessens emotional distress. Beyond these outcomes, palliative care also helps with more equitable resource utilization by identifying patients for whom aggressive curative measures are either unwarranted or unwanted. As a result, patients receiving palliative care—and their families—make different choices, resulting in reduced hospitalizations and intensive care unit (ICU) admissions, and consequently in cost savings.[2]

Evidence pointing to the benefits of involving palliative care earlier in oncology cases continues to grow. In one seminal study conducted in an ambulatory oncology clinic, published in 2010, patients newly diagnosed with stage IV non-small cell lung cancer (NSCLC) were randomized to either regular oncology care or an experimental group that got palliative care *concurrent* with regular oncology care. Quality of life, mood, and survival were measured at baseline and at 12 weeks after treatment. Another measured parameter was "aggressive care," defined as chemotherapy within 2 weeks of death or later or no hospice admission. Patients who received both palliative care and regular oncology care had significantly higher quality of life scores, were less depressed, and sought less aggressive care. Interestingly, de-

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spite receiving less aggressive care, those patients lived an average of 2.7 months longer.[3] More recent studies have shown that early palliative care for cancer patients is associated with earlier do-not-resuscitate designations and less frequent ICU deaths.[4] Earlier palliative care referral has also been associated with fewer emergency department visits, hospitalizations, and hospital deaths.[5]

Why these results? One explanation is that a palliative care referral can lead to reduced use of chemotherapy or other treatment in the last days or weeks of life. During such a referral, patients and families have the chance to share their personal goals and priorities while also being offered the full range of treatment options, including palliative or supportive care and, if appropriate, hospice. When palliative care providers ask patients where they want to die or how they want to spend their remaining time, fewer patients choose the hospital or the ICU. This is critical, because if we do not seek patient preferences or fail to give them the full range of choices including palliative care, those who continue on aggressive treatments like chemotherapy in the last weeks of life have an increased risk of undergoing CPR, of being on a ventilator, and of dying in an ICU.[6] This is probably not the preferred scenario of patient or family. In his best-selling book, *Being Mortal: Medicine and What Matters in the End*, Atul Gawande, MD, MPH, discusses the importance of asking these key questions.[7]

In this evolving landscape, the American Society of Clinical Oncology (ASCO) issued a Provisional Clinical Opinion in 2012 calling for the integration of palliative care into standard oncology care,[8] including the guideline that people with metastatic NSCLC should be offered concurrent palliative care and standard oncologic care at initial diagnosis. Generally, for other cancers, ASCO's position is that evidence suggests that combining palliative care with oncologic care leads to better patient and family outcomes, with no harm to either party, and that no excessive costs accrue from early palliative care involvement.[8] The ASCO expert consensus is summarized in the **TABLE**.

The Institute of Medicine, in its 2013 Report on Cancer Care, called for palliative care to occur at the beginning of the cancer continuum, at diagnosis, then continue through treatment, survivorship and, if need be, end-of-life care.[9] One rationale for offering palliative care to oncology patients undergoing active treatment is that it can help them better tolerate and complete that treatment, which results in improved outcomes and a better chance for survival. For example, in a case I am familiar with, a 45-year-old woman was diagnosed with an aggressive form of B-cell lymphoma several months after she gave birth to twins. She received the standard chemotherapy protocol at a leading cancer center, which put her cancer into remission. Unfortunately, she relapsed 18 months later and underwent an autologous stem-cell transplant. While at the cancer center for induction, she developed intractable nausea and, though already thin, lost much weight. She also had pain and found it emotionally trying to be away from her family, about whom she was understandably worried.

TABLE. ASCO Expert Consensus on Standard Oncology Care and Palliative Care[8]

1. Combined standard oncology care and palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden.
2. Strategies to optimize concurrent palliative care and standard oncology care, with evaluation of its impact on important patient and caregiver outcomes (eg, quality of life, survival, health care services utilization, and costs) and on society, should be an area of intense research.

At a friend's suggestion, she asked her oncology team to consult the cancer center's palliative care service. Her team initially felt this wasn't appropriate, because her death wasn't likely, but the patient's concern was that she *would* die if the nausea and other issues weren't addressed. Acceding to her wishes, the palliative care team was consulted. They got her nausea and pain under control, provided emotional and spiritual support, and even helped her get an absentee ballot for an important election. She made it successfully through the transplant and is still in remission 4 years later. While palliative care was not solely responsible for her good outcome, this patient will assure you it played an important role.

But this case study also showcases the barriers patients and families can face when seeking palliative care services. Unfortunately, many clinicians think palliative care is only for dying patients and they avoid considering or recommending it until the final days.[2,10] In an attitudinal research study of physicians, they described palliative care as "comfort care" for dying patients.[11] None thought it was appropriate earlier in a serious illness.[11] This is ironic, as many physicians in other studies have acknowledged that they would not choose aggressive care themselves, were they to be seriously ill.[12]

IMPROVING ACCESS TO PALLIATIVE CARE

Among the ways palliative care can be made more accessible to oncology patients are:

- Oncology practices can develop partnerships with palliative care services in their health systems or geographic areas. Such resources are increasing, with certifications for palliative physicians, advance practice nurses, and nurses. The certification training makes these care providers particularly adept at symptom assessment, management, and communication. Most cancer centers and large hospitals have palliative and supportive care services, the staffs of which are happy to work more collaboratively with their oncology partners. More pharmacists can receive palliative care training to support the management of complicated medication regimens.
- While palliative care is still developing in the outpatient arena, it can prove quite beneficial. In one study involving a palliative care–certified physician and nurse practitioner who joined forces with an oncology clinic, palliative care referrals increased 87% and symptom burden among the clinic's patients decreased 21%.[13] What's more, the clinic's oncologists rated their satisfaction with the palliative care service as 9 on a scale of 10, and each palliative care referral saved, on average, 170 minutes of their time.[13]
- Oncology clinicians can be trained to provide primary palliative care themselves—just as clinicians are expected to have basic proficiency in, say, cardiology or nephrology, with specialists available to handle more complex cases. For palliative care to become a standard part of oncology care, all oncology clinicians would need to learn the requisite skills of communication and of symptom assessment/management, and to learn to provide emotional and spiritual support for their patients. Of course, many already do, and their teams may include such patient- and family-support resources as social workers, case managers, and chaplains. However, this is not always the case. Sometimes the oncologist alone has to help a challenging patient or family, and primary palliative care training would be invaluable.

If palliative care becomes part of standard oncology care, then patients and families will no longer worry that receiving such treatment means they are dying. Instead, they will appreciate providers who are trained to listen to them, who solicit their values and goals, and who partner with them when making important medical treatment decisions. The improved outcomes that result will benefit us all. **EBO**

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How and Why Oncologists Should Do Palliative Care—or Get Some Assistance Doing It

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From a policy perspective, the Affordable Care Act contains language addressing end-of-life care costs. Despite this increased attention, care at the end of life is getting more aggressive, with more intensive care unit use and transitions to different sites of care, and later and shorter use of hospice.

INTRODUCTION

Americans are more aware than ever that care at the end of life is often costly, poorly coordinated, and not aligned with patients' wishes. Multiple news outlets have published stories in the past year chronicling the gap between patients' preferences and the care they actually receive, particularly when their disease is incurable.[1,2] In September 2014, the Institute of Medicine (IOM) released a report calling for the fundamental overhaul of end-of-life care.[3] From a policy perspective, the Affordable Care Act contains language addressing end-of-life care costs.[4] Despite this increased attention, care at the end of life is getting more aggressive, with more intensive care unit use and transitions to different sites of care, and later and shorter use of hospice. These trends often run contrary to patients' expressed wishes.[5]

One of the keys to closing this gap and altering the worrisome trend is the earlier incorporation of palliative care services into a patient's care plan. This integration is particularly important in the care of oncology patients, whose illnesses may be terminal and fraught with severe symptoms. Though many oncologists believe that their practice already successfully incorporates palliative care, the available evidence suggests that they are wrong in some cases. In a recent study, oncologists rated their skill in managing cancer pain higher than pain specialists rated their own; however, oncologists had lower scores in managing 4 common complex pain problems on standardized vignettes.[6] Nearly half of oncologists are reluctant to refer complex pain patients to pain specialists, despite performing worse than pain specialists on pain vignettes.[6] From a patient education perspective, one study found that less than one-fifth of patients with terminal colorectal or lung cancer managed by community oncologists could correctly repeat the prognosis their oncologist had given them.[7]

These studies suggest a substantial discrepancy between the care oncologists perceive they are providing and the quality of care being delivered. In this commentary, we address ways to remedy this gap through our review of the evidence for earlier and more comprehensive integration of palliative care with oncologic care.

BENEFITS OF EARLY PALLIATIVE CARE INVOLVEMENT

The benefits of palliative care are clear, important, and broad—and their impact is stronger when palliative care begins early. Demonstrated benefits for the patient include improved symptom management, increased satisfaction and quality of life, decreased depression and anxiety, and even improved survival. Demonstrated benefits for the healthcare system include fewer readmissions and markedly lower costs per day. We have summarized these findings from recent research in **TABLE 1.**

Building on these findings, the American Society of Clinical Oncology (ASCO) published a provisional clinical opinion in 2012 regarding the integration of palliative care services into standard oncology practice when a patient is diagnosed with metastatic or advanced cancer.[17] The panel made a strong recommendation that "Combined standard oncology care and palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden."[16] Partially stemming from these recommendations, in 2013, the Agency for Healthcare Research and Quality funded a collaboration between ASCO and the American Academy of Hospice and Palliative Medicine to develop and disseminate a primary palliative care evidence-based curriculum for oncology and to study the curriculum's effect on the quality of care through the use of embedded quality metrics in the oncology measure set.[18] While these recommendations are helpful for practitioners, the onus falls on individual practitioners to incorporate changes into their practice.

Beyond the evidence and societal recommendations, our own clinical experiences at Sydney Kimmel Comprehensive Cancer Centre suggest that early involvement of palliative care allows for the ongoing assessment of patients' wishes as they evolve through the course of their illness. These repeated discussions inform clinical preparedness and planning prior to the onset of disease-induced disability, and also serve as an extra layer of support to the patient and his/her loved ones in conjunction with treatment and follow-up sessions.

TRENDS IN PALLIATIVE CARE PRACTICE

Palliative care is a growing field, and while more and more practitioners are being trained in this specialty, there is a dearth of specialists available to meet the increasing demand. Integration of palliative care into other practices, including and beyond oncology, will be crucial to addressing this need.

Lack of Trained Specialists

Since the field's recognition as a subspecialty in 2007, fellowship-trained palliative physicians and allied professionals have increased in number. As of 2013, there were about 5000 board-certified palliative care specialists in the United States,[18] and as of 2015, there are 11,000 nurses registered with the Hospice & Palliative Nurses Association.[19] Despite the increasing number of practitioners, the number of facilities wherein people can be certified is relatively limited. For example, in 2010, there were only 73 accredited allopathic subspecialty training fellowship programs that collectively produced approximately 86 new palliative medicine physicians per year.[20] In the past 10 years, however, the number of in-hospital palliative care teams and inpatient units has increased. The number of palliative care teams within hospitals in the United States, with 50 or more beds, has grown 164%—from 658 in the year 2000 (which was less than one-fourth of US hospitals) to more than 1700 in 2012.[21] Nearly 67% (1734) offered these services in 2012.[21]

The increase in the number of palliative care physicians is still not enough to meet current demand. For example, as of 2011, there was 1 oncologist for every 141

TABLE 1. Randomized Trials of Early Specialty Palliative Care Interventions in Patients With Cancer

	POPULATION	INTERVENTION	RESULTS	MOST SURPRISING FINDING
Brumley[8]	298 homebound patients with a prognosis of <1 year and a recent hospital or ED admission; included 138 patients with cancer	Usual care plus in-home multidisciplinary PC (frequency of visits based on individual need of patients) vs usual care	Patients assigned to PC had lower rates of ED (P = .01) and hospital admissions (P <.01), decreased medical costs by $7552 ($P$ = .03), and were more likely to die at home (P <.01). No difference in hospice enrollment	People lived just as long, but better, and cost Kaiser Permanente $7552 less per person, even including the cost of the IDPCT.
Gade[9]	517 patients with at least 1 life-limiting diagnosis and their physician indicating they "would not be surprised if the patient died within 1 year"; included 159 patients with cancer	Usual care plus inpatient multidisciplinary PC consultation vs usual care	Patients receiving PC reported better care satisfaction (P <.01), had fewer ICU stays on hospital readmission (P = .04), and were responsible for, on average, a 6-month net cost savings of $4855 per patient ($P$ <.01). No differences in hospice use, completion of advanced directives, symptoms/QOL, or survival	After this 2nd study, Kaiser Permanente made IDPCTs part of its usual care in every large market.
Finn (published only in abstract form)[10]	165 patients who were seriously ill with cancer and had a 50% chance of dying within 6 months	Usual care plus IDPCT (including supportive services from a leading hospice program) vs usual care	Preliminary findings showed patients receiving PC had little difference in symptom control, but lived slightly longer (266 vs 227 days, NS), had more relief of caregiver burden (P = .06), had better quality of life (P = .08), had higher reported pain scores (P = .14), and used less resources ($7059 difference) (adjusted for mean duration of 250 days, due to fewer hospitalizations, P = .3). Later analysis showed reduced caregiver burden, a 27% cost savings in the intervention group, and a difference in symptom burden. The project was terminated by the Hospice of Michigan as the longer length of stay in hospice (average 4.7 months) did not offset the cost of chemotherapy drugs and care. The study has never been published in its entirety.	PC led to reduction in caregiver burden and a 27% cost savings in the intervention group.
Bakitas[11]	322 patients with a life-limiting cancer and a prognosis <1 year as identified at tumor boards	Usual care plus phone-based PC administered by NP in 4 structured sessions and > monthly follow-ups vs usual care	Patients assigned to PC reported better quality of life (P = .02) and mood (P = .02). No differences in symptom burden or intensity of service (hospital and ICU days or number of ED visits)	
Temel[12,13]	151 patients within 8 weeks of diagnosis of metastatic lung cancer	Usual care plus outpatient PC (provided by MD or NP) >monthly and PC consult when hospitalized vs usual care	Patients receiving early PC had better quality of life (P = .03), lower rates of depression (P = .01), less aggressive EOL care (P = .05), and longer median survival (P = .02).	The PC patients were more accepting of their life-ending illness, but had lower (by about half) levels of depression and anxiety, and lived 2.7 months longer.
Zimmermann[14]	461 patients with stage IV cancer, European Cooperative Oncology Group performance status of 0-2, and a prognosis of 6-24 months; 393 patients completed at least 1 follow-up assessment	Usual care plus consultation and follow-up (at least monthly) with a PC team vs usual care	At 3 months, patients receiving the intervention did not have a significant difference in improved QOL (P = .07), but did have significantly improved QOL at EOL (P = .05) and improved patient satisfaction with care (P = .0003). No difference in symptom severity and problems with medical interventions. At 4 months, patients receiving the intervention had significant differences in change scores for all outcomes except problems with medical interventions.	Early PC might improve QOL and increase satisfaction with care for patients with a large range of advanced solid tumor malignancies. The core intervention involved outpatient consultation and follow-up by a palliative care physician and nurse; the hospital's palliative care clinic began as a half-day clinic per week, which was not a large drain on existing inpatient palliative care resources (cost analysis forthcoming).
Bakitas ASCO 2014[15,16]	207 patients with recurrent or metastatic cancer and 122 family caregivers (family caregivers were defined as "someone who knows you well and is involved in your medical care")	Immediate entry into ENABLE (Educate, Nurture, Advise, Before Life Ends), a phone-based concurrent oncology palliative care intervention vs delayed entry into ENABLE (initiated 12 weeks after randomization)	Caregivers' estimated treatment effects (ie, from immediate compared with delayed intervention) for randomization to 12 weeks had trends towards improved quality of life (P = .17), lower depression (P = .003), and lower subjective burden (SB) (P = .02). Caregivers' estimated treatment effects from intervention initiation to 12 weeks were trends toward improved QOL (P = .06), lower depression (P <.001), and lower SB (P = .08). Caregivers' estimated treatment effects measured backward from the time of patient's death were trends toward improved QOL (P = .07), lower depression (P = .02), and lower SB (P = .01).	Caregivers who received the intervention closest to diagnosis had lower depression, lower SB, and trends toward better QOL; this suggests concurrent oncology palliative care should be initiated at or near diagnosis to maximize benefit to caregivers.

ED indicates emergency department; EOL, end of life; ICU, intensive care unit; IDPCT, interdisciplinary palliative care team; MD, physician; NP, nurse practitioner; NS, not significant; PC, palliative care; QOL, quality of life; SB, subjective burden.

TABLE 2. Primary Palliative Care Skills Every Oncologist Should Have

Basic management of pain and other symptoms due to cancer and its treatment
Basic management of depression and anxiety
Empathic communication skills • What is your understanding of your situation?[23] • How do you like to get medical information? • What is important to you? • What are you hopeful for?
Basic discussions about: • Prognosis • Goals of treatment, which are rarely done even at academic centers[24] • Suffering • Code status and resuscitation, with appropriate information about surviving CPR, and suggestions for patients.[25]

Modified from Quill and Abernethy[18]

TABLE 3. Questions to Start the Conversation

- Are you bothered by (symptom)? (This is a safe and comfortable way to start)
- What are the most important things in your life right now?
- What are you hopeful about?
- Are there things about your current situation that frighten or disturb you?
- What is your understanding of your illness?
- Is spirituality an important part of your life?
- Do you understand your prognosis? [a]
- What are your goals as time runs out? [a]
- What trade-offs are you willing to make? [a]
- How do you want to spend your time if your health worsens? [a]
- Who do you want to make decisions for you if you are unable to do so? [a]

[a]Adapted from Susan Block, MD, at the Dana-Farber Institute, as quoted in Gawande A. Being Mortal. *In: Being Mortal: Medicine and What Matters in the End.* New York: Metropolitan Books; 2014:182-183.

newly diagnosed cancer patients in the United States, but only 1 palliative medicine physician for every 1200 persons living with a serious or life-threatening illness.[22] There is a clear need to either train more physicians or develop alternative approaches. Johns Hopkins currently has 4 fellows, and we are starting to teach primary palliative care skills to all physicians and advance practice nurses.

Since the 1990s, advocates have pushed for all healthcare practitioners to receive training in basic palliative care skills (eg, the Education in Palliative and End-of-Life Care and End-of-Life Nursing Education Consortium courses).[18] However, the increased demand for palliative care has led experts to call for a "reenergized, concerted effort spanning the health care system."[18] Stemming from this need, in a 2013 opinion piece in *The New England Journal of Medicine*, Quill and Abernethy advocated for each medical specialty and health system to "delineate basic expectations regarding primary palliative care skills to be learned and practiced by its members, plus a triage system for calling on palliative care specialists when necessary."[18] In addition, they maintained that these defined palliative skills would be distinguishable from palliative care requiring formal consultation.[18] Quill and Abernethy explored how this shift would simplify the healthcare system, enhance clinicians' skills, increase patient satisfaction by enabling deeper patient-provider relationships, and help control costs through reducing the number of specialists comanaging patients.[18] The expansion of palliative care is an ongoing conversation in the field and reinforces the evidence supporting earlier integration of palliative care into oncology practice. Building on the Quill and Abernethy commentary, in **TABLE 2** we have included our suggestions regarding necessary primary palliative skills for oncologists.

In addition to training healthcare practitioners, there is a push to introduce this training into school curricula. For example, starting as early as 1996, the University of Rochester School of Medicine in New York introduced a fully integrated comprehensive palliative care curriculum,[26] and at Johns Hopkins School of Medicine all medical students must complete a 4-day intensive course entitled *End of Life and Palliative Care* before graduation.

HOW TO ALLEVIATE BARRIERS TO EXPANDING PALLIATIVE CARE

There are barriers that the healthcare system must overcome to truly integrate palliative care components into oncology at the time of diagnosis. First, we must strive to dispel myths among patients and providers that palliative care is a death sentence or a sign that the physician has given up on a patient. The time for intervention within oncology is not just upon the penultimate or antepenultimate admission. Palliative care should not be considered a fourth-line treatment, but rather a first-line treatment. These misunderstandings can only be dispelled through education and discussion.

There is not a single study to date that shows decreased survival with a palliative care intervention, which debunks some providers' concerns and stigmas regarding palliative care. In fact, at least 2 additional studies have shown a significant survival benefit to symptom management and palliative care in addition to usual care. In addition to the Temel and ENABLE-III trials discussed in Table 1, Smith and colleagues randomized 202 patients with severe refractory cancer pain to best medical management by a trained expert team to the same care plus an intrathecal drug delivery system (IDDS). Members of the IDDS group had significantly better pain control, fewer drug toxicities, and lived an average of 102 days longer.[27] In another study, Higginson and colleagues randomized 105 patients with severe breathlessness to usual pulmonary care versus usual care plus an interdisciplinary palliative care team (IDPCT) integrating palliative care, respiratory medicine, physiotherapy, and occupational therapy. The primary end point was mastery of breathlessness at 6 weeks, which was achieved. Additionally, survival was improved at the 6-month mark: 94% in the intervention group versus 75% in the control group (P = .048).[28] These studies underscore the survival benefit with palliative care.

Second, we must strive to create a collegial environment wherein practitioners work together to support a patient across the continuum of care, as opposed to territorial tensions. Even in lung cancer, where there is substantial evidence of benefit, only 8% of patients are seen by a palliative care team, usually near death, to address end-of-life issues.[29] Third, we must strive to consistently introduce early palliative care among oncology patients, and more regularly invoke palliative care help and consultation. Over 60% of all oncology hospital admissions are due to symptoms, and admission for a symptom should be an automatic consult request.[30]

Finally, an overarching barrier is institutional resistance to change. Research suggests that early integration of palliative care into oncology care can profoundly affect a healthcare facility. For example, in a pilot study at the Division of Hematology/Oncology, Tisch Cancer Institute, Icahn School of Medicine, outcomes improved when palliative care consultations were mandated for patients with stage IV disease or stage III lung or pancreatic cancer, a prior hospitalization within the past 30 days, hospitalization for more than 5 days, or uncontrolled symptoms (pain, nausea, dyspnea, delirium, or distress).[31] Palliative care consultations doubled from 41% to 82%, 30-day readmissions dropped from 36% to 17% (*P* = .022), hospice utilization increased from 14% to 25% (*P* = .146), and mortality index improved (1.35 to 0.59). When the program stopped after the 3-month trial, the oncologists demanded its return! Similar programs are in the plans at Johns Hopkins for when more personnel are in place.

These barriers can be overcome and we can learn from leading practices across the country and abroad.

CONCLUSION

Despite the obstacles explored above, integration of palliative care into oncology care is an evidence-based practice, bolstered by recent studies and the ASCO recommendations. This movement in care is broadly aligned with trends in palliative care as well as discussions occurring in public discourse. Early palliative care involvement is a rare example of a medical win-win solution: for the patient, his/her caregiver, the physician, the hospital, and the healthcare system as a whole. **EBO**

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TABLE 4. Ten Steps to Guide Your Palliative Care Practice and Conversations

1. Use the ask, tell, ask method

a. Always ask people how much they want to know, and what they do know about their diagnosis.
b. Then tell them, in language they can understand. Don't be afraid to make recommendations.
c. Afterwards, ask about their comprehension of what you have told them.
d. Help the patient to cultivate prognostic awareness by asking him or her to imagine a poorer health state.[32]

2. Recognize that denial does not necessarily mean a person is unhealthily coping with the reality of his or her prognosis, but is rather a tool for patients to integrate the reality of their death over time.[33]

a. If a patient's disease is stable, but the patient is ambivalent about a prognosis discussion, cultivate prognostic awareness at a later time.[32]
b. If a patient's disease is worsening but the patient is ambivalent, acknowledge to the patient that it is hard to discuss their prognosis while also articulating the disadvantages of avoiding that discussion.[32]
c. If a patient is ready to discuss their prognosis, convey the information using the ask, tell, ask method.[32]

3. Take advantage of decision aids to provide an accurate prognosis to patients who want to know it.

4. At each transition point, when changing treatment or prognosis, ask about the patient's understanding of their situation, and ask what the patient is hoping for.

5. Always do a symptom assessment.

a. Ask about pain, tiredness, nausea, depression, anxiety, drowsiness, anorexia, constipation, dyspnea, and secretions.

6. In at least some cases, do a spiritual assessment. If the patient is spiritual, consider using the AMEN approach in working with him or her[34]:

a. Affirm the patient's belief:
   i. "Ms. X, I am hopeful, too."
b. Meet the patient or family member where they are:
   i. "I join you in hoping (or praying) for a miracle."
c. Educate from your role as a medical provider:
   i. "And I want to speak to you about some medical issues." (Do not use the word "but," which puts you in opposition to God. And you may need her to do your neurosurgery some day.)
d. No matter what, assure the patient and family that you are committed to them: "No matter what happens, I will be with you every step of the way." This specific statement of non-abandonment is critically important to patients.[35]

7. Make a hospice referral when the patient still has 3 to 6 months to live.

8. Audit hospice referrals, as the Quality Oncology Practice Initiative does.

9. Have a plan in place for seriously ill patients who have less than 1 year to live.

10. Use some palliative care "pearls" in your practice.

a. Olanzapine for nausea.
b. Ginger for nausea and fatigue.
c. Dexamethasone for fatigue and better quality of life.
d. American ginseng 2000 mg a day for fatigue.

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Palliative and End-of-Life Care: Issues, Challenges, and Possible Solutions in the United States

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INTRODUCTION

With Baby Boomers outnumbering children less than 5 years of age in the United States, society as a whole, and those in the medical field in particular, are faced with aging-related challenges moving to the forefront. While some are inevitable, others are self-created or might even be politically motivated. Yet as science evolves from the macro down to the nano level, we have had some difficulty embracing a key concept: physicians can diagnose disease by molecular rearrangements using gene microarrays, and yet we as a society are unable to come to a common understanding that death is an inevitable continuum of life. Every single living organism is destined, indeed genetically programmed, to die. And yet, despite all of our advances, neither the larger scientific community nor society as a whole is willing to initiate a sustainable debate around death—the only certain facet of existence. This lack of effort and willingness to accept, study, research, and implement appropriate intervention alongside the process of death and dying has often led to appalling quality of care in the last few weeks or months of a patient's life, extreme financial burdens, and lasting psychological issues for caregivers.

The United States devotes more money and resources to healthcare than any other country in the world, at 16% of gross domestic product (GDP). In fact, the amount of money spent on healthcare here exceeds the total GDP of most countries in the world except for China, Germany, and Japan. Yet, despite the massive deployment of resources, we do not lead the ranking in the majority of indices for healthcare matrices. The United States lags behind 20 other nations in life expectancy and its quality-of-death index is below that of a majority of developed European nations. One-third of all expenditures from federally funded programs are spent in the last year of life and within that last year, one-third of resources are spent in the last month of life.[1,2]

CHALLENGES UNIQUE TO THE UNITED STATES

The United States is a unique, multicultural society: multitudes of ethnicities live side by side, each practicing and following its own distinct faith and set of end-of-life beliefs. This fact, combined with several special interest groups, scientific advancements, and slogans like "conquer cancer," "cheat death," and "beat the disease" have created an environment of unrealistic expectations among the general populace, up to and including the educated elite. Our unrealistic mind-set of living forever is compounded by the fact that we see terminal and life-threatening illnesses as enemies to be conquered. The "War on Cancer," a term coined during the Nixon administration, has morphed into modern slogans of battles against the disease.

Unfortunately, this all represents a collective loss of our sense of reality. First and foremost, the basic biological nature of cancer as a mutation of one's own tissues has largely been ignored in the mindset of the general populace. Rather, cancer is represented as an outside enemy force that needs to be vanquished. Cries of "Conquer!," though well-meaning, can have shocking reverberations, especially in patients who are "losing" their fight—it can darken, even demoralize the human spirit at its most vulnerable time. Rather than acknowledging cancer as a mutation in one's body, the suffering patient feels stigmatized, as their spirit and belief in a moral strength are measured by the degree of "success" in their fight against cancer.

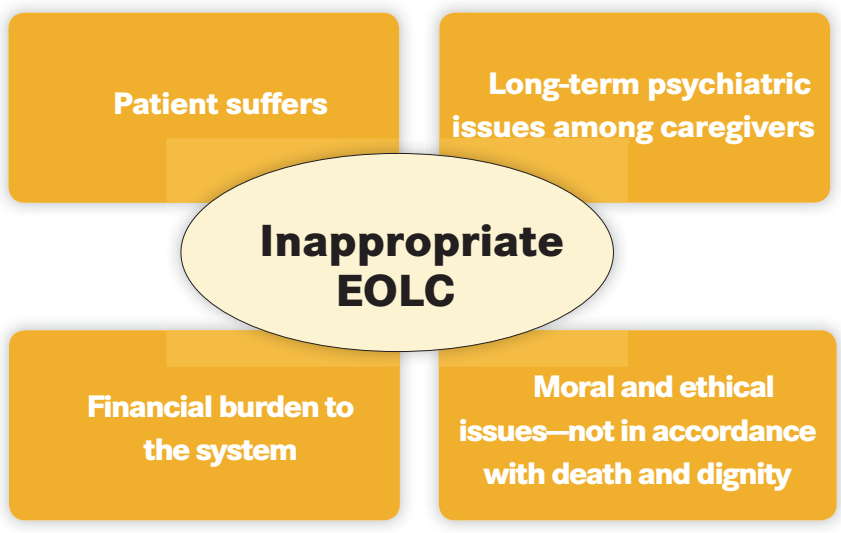
Almost always in terminal cases, this warlike mentality triggers an excessive pursuit of marginal improvements in life expectancy. Sadly, the only thing greater than the financial expenditure thus endured near the end of life is the pain and suffering that the terminal patient must withstand for minor, and sometimes even nonexistent, improvements in life expectancy. Instead of facing imminent death in a comfortable environment with suffering that is compassionately managed to improve quality of life, the patient experiences near-constant discomfort and lives out his final few days hooked to a drip in a hospital bed. The primary loser is the dying individual, and the secondary loser is the larger society: we bear these costs when they are virtually without benefit (and often at significant detriment) to the individual whom they were meant to assist.

Further compounding the problem is the egotistical attitude many treating physicians develop: They count themselves as "winners" or "losers" depending on a treatment's outcome, eventually forgetting on some level the simple fact that everyone will die at some point. Indeed, physicians and researchers alike often perceive death and dying as a failure of their efforts versus a natural process of degeneration.

Complicating the matter further, any debate about compensating doctors to address end-of-life care (EOLC) rapidly devolves into laced jargon and "death panel" terminology. The effect is so strong, and there is such implicit emphasis upon borderline immortality as an achievable goal for a physician, that fewer than 10% of medical schools offer education on the process of death and dying to their students, and fewer than 18% of medical students and residents (according to 1 survey) have received formal EOLC education. Approximately 39% felt unprepared to address patients' fears about death, and nearly 50% felt unprepared to manage their own feelings about it. Forty percent felt that dying patients were not considered good teaching cases and that meeting the psychosocial needs of dying patients was not a core competency.[3]

Healthcare in the United States, in general, focuses on identifying and treating the abnormal findings within an individual rather than on the holistic treatment of a multidimensional human being. Homing in on diseased tissue has, all too often, overridden the human context within which medicine should be practiced. The typical 2-minute interaction of a patient and inten-

FIGURE. Consequences of Inappropriate End-of-Life Care (EOLC)



sivist in the intensive care unit (ICU), where measuring electrolytes and respiratory and cardiac parameters take precedence over any other aspects of the patient's condition, exemplifies the elevation of science over humanity. As the typical ICU is structured, there is little space to explore, understand, respect, or implement an individual patient's desire, which indicates a fundamental flaw in the culture of hospital medicine that can be addressed only by understanding and exploring hospital functional culture.[4]

The financial and societal consequences of inordinate end-of-life expenditures abound. Studies indicate that patients who died in the ICU had significantly worse quality of life than those who died at home; their caregivers, too, have exhibited persistent psychological issues (**Table**).[5] What's more, there is evidence that when EOLC and advanced care planning were mentioned during physician-patient communications, acceptance of hospice and comfort care as well as palliative care was significantly higher and, consequently, less expensive.[6]

Significantly, physicians who are able to remain engaged and "present" for their dying patients—by inviting and answering questions, and by treating patients such that they feel they matter as fellow human beings—have the capacity to improve a dying patient's quality of life.[7]

Physicians and oncologists also face personal issues in dealing with death and dying. As a large study conducted in 3 Canadian hospitals indicates,[8] more than half of oncologists struggle with feelings of failure, self-doubt, sadness, and powerlessness. Unacknowledged grief among these oncologists has at times led to inattentiveness, impatience, irritability, emotional exhaustion, and burnout. They can distance themselves and withdraw from those patients who are closer to dying. A similar percentage of physicians reported that unaddressed grief altered the treatment decisions they made with subsequent patients, resulting in more aggressive treatment and reluctance to recommend palliative care or hospice. Such individual factors also result in some oncologists' reluctance to initiate and address EOLC.

TABLE. Challenges and Solutions for Healthcare in the United States

PROBLEMATIC ISSUES	SOLUTIONS
SCIENCE OF MEDICINE	
• Measures quanity over quality	• Design studies measuring quality
• Ignores humane aspect	• Consider psychological factors
• Seeks primary objective	• Incorporate subjective parameters
• Death viewed as a severe toxicity	• Death is a natural evolution of life
HEALTHCARE CULTURE	
• Hierarchical	• Place patient at the center of control
• Territorial and fragmented	• Multidisciplinary approach
• Poor communication between disciplines	• Start "EOLC support groups"
• Unrealistic expectations	• Accept death as natural process
PERSONAL FACTORS	
• Unhealed grief	• Recognize physician grief as real entity and offer counseling and help
• Denial of death	• Replace "battle and conquer"
• Fear of the unknown	• Counseling for physicians
SYSTEM OF MEDICINE	
• Time limitations	• Offer chronic care management fees
• Lack of reimbursement	• Compensate for EOLC counselling
• Medicare regulations	• Payment reforms
• Malpractice litigation	• Recognize death as natural process
• Lack of training in medical schools	• Make EOLC mandatory in medical schools

EOLC indicates end-of-life care.

ISSUES AFFECTING EOLC

The World Health Organization has defined palliative care as "an approach that improves the quality of life of patients and their family members facing the problems associated with life-threatening illness, through the prevention and relief of suffering." However, due to several factors—among them the reluctance of society to accept death as a natural process, excessive medicalization, and emphasis on defeating disease—discussions of palliative care remain all too rare.

The limited research on EOLC reveals that a multifactorial approach is best to address the challenges of providing appropriate palliative care and EOLC in the United States. According to findings published in the large multicenter Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT), physicians were largely unaware of their patients' EOLC preferences (eg, do not resuscitate/do not intubate orders).[9]

Critics argue, at times, that embracing EOLC is akin to abandoning patients—a narrow-minded view, we feel, similar to the belief that length of life is the exclusive metric of physician success. Embracing EOLC is in no way akin to giving up on patients. Rather, it complements existing treatment protocols. If treatment fails and a patient is still terminal, appropriate EOLC should be an option presented for serious consideration. The patient needs to know they have the right to choose between extending treatment that could squeeze out a few more weeks or months of survival but have serious impact on quality of life, or to elect EOLC, designed to improve quality of life toward the end.

While patient autonomy is acknowledged as a key cornerstone of medicine, it has fallen by the wayside where EOLC is concerned. Most often, patients have neither explored the need for planning for their death nor are fully informed about the consequences of medical interventions. Although every state requires that patients admitted to hospitals be asked if they have advanced directives, it has devolved into a check-the-box exercise that is quickly fulfilled in the emergency department triage area. Simply passing legislation cannot bring about cultural change. Discussions about advanced care planning, palliative care, and EOLC are much more meaningful when carried out with a physician—a family doctor or subspecialist involved in chronic disease management—familiar with the patient.

THE WAY FORWARD

In summary, EOLC in the United States faces many challenges. In a recent report, the Institute of Medicine highlighted the magnitude of the problem and delivered many recommendations including those in the realms of healthcare delivery, professional education and development, policy decisions and development, public education and awareness, and payment reform. The report identified the deficit in palliative care education in medical and nursing school curricula as well as the deficit in physician communication skills.[10]

The foundations of suitable EOLC and improvement in quality of death are rooted in physician-patient communication. Improving the overall quality of death for a multicultural society like the United States rests on awareness among healthcare providers of cultural and ethnic preferences and of beliefs related to death and dying. Educating providers about these attitudes would result in enhanced trust, confidence, and patient acceptance of appropriate EOLC. As stated previously, improved communication about advance directives, EOLC, and comfort care result in acceptance of better EOLC, improved quality of life, and reduced healthcare expenditure.

Another necessary, significant step is to remove politics from the EOLC conversation. As much as we want to respect individual freedom and autonomy, hijacking a real debate on EOLC for sheer political gain not only causes disservice to patients, but to society as a whole. This may partially explain why, despite spending hundreds of billions of dollars, our nation still lags behind many developed countries in both quantity of life and quality of death.

Finally, we want to embrace death not as a failure for a physician, but rather as a natural process that all of us will face one day. Let us no longer stigmatize death as our failure. **EBO**

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Global Outlook on Palliative Care in Cancer

Megan O'Brien, PhD

INTRODUCTION

Palliative care, and effective pain relief in particular, is a core component of cancer treatment. It's been estimated that approximately 80% of people with advanced cancer require opioids to treat moderate or severe pain.[1] However, access to medicinal opioids varies widely across the globe, with access generally proportional to a country's gross income level.

Cancer and HIV are the 2 leading indications for opioid use. Low- and middle-income countries are home to 71% of cancer deaths[2] and more than 99% of deaths from HIV,[3,4] yet they consume less than 7% of the world's medicinal opioids.[5]

Among the 175 countries that have data available on cause of death and opioid consumption, 60 consume a quantity of opioids that is not sufficient to meet even 10% of their need, with 40 of those countries in sub-Saharan Africa.

Worldwide, at least 2.4 million people die with untreated pain from cancer or HIV each year—lack of access to effective pain relief and palliative care is responsible for a tremendous amount of unnecessary suffering. Importantly, the high rate of stigma associated with these diseases results in turn in late presentation and poor treatment outcomes. For instance, in low-income countries, the majority of cancer diagnoses occur when patients' disease is already advanced.[6,7] While several factors contribute to delayed diagnosis—limited access to healthcare, limited diagnostic capacity of health systems, and inability of patients to afford even the most nominal costs associated with investigations—patients also present late because cancer, as a disease, is synonymous with unrelenting pain that grows worse each day. Patients fear the diagnosis and they do not expect hospitals to provide them with pain relief.

This suffering is unnecessary, because morphine is safe, effective, plentiful, inexpensive, and easy to use in resource-limited settings. Morphine has been designated an essential medicine by the World Health Organization (WHO)[8] and is on almost all national essential medicines lists. Morphine and similar opioids are the only treatments for moderate or severe pain recommended by WHO in its pain treatment guidelines.[9] Additionally, WHO has also developed a simple algorithm for pain treatment that is 80% to 90% effective: the analgesic ladder. The approach, which includes a 3-step algorithm for adults and a recently updated 2-step algorithm for treatment of pain in children, utilizes both opioid and non-opioid medicines.[10]

Derived from a plentiful plant source, morphine is off-patent, and thus quite affordable. An average weekly dose of treatment (67.5 mg per day)[1] costs less than $1 (based on recent procurements in Uganda, Kenya, Swaziland, and Nigeria). The existence of an essential medicine that is so well suited to relieving pain in resource-limited settings makes the suffering caused by an inability to access the medicine both unnecessary and preventable.

BARRIERS TO ACCESS

The tremendous disparity in the lack of access to pain relief and palliative care is driven by several factors operating at different degrees in different settings.

In many countries, opioids such as morphine are not imported because ministries of health are structured around disease-specific units. Pain relief cuts across diseases (and accidents, childbirth, and postoperative care) in a way that causes it to fall between the cracks, not squarely in the mandate of any single department.

Pain relief is often given low priority within health ministries and particularly within oncology departments because of a cure-versus-care mentality that places higher value on interventions that have the potential to cure disease or extend survival.

Pain relief is often given low priority within health ministries and particularly within oncology departments because of a cure-versus-care mentality that places higher value on interventions that have the potential to cure disease or extend survival; interventions that improve the quality of life are often considered optional and there is little precedence for their use in resource-limited settings.

Even when health ministries commit to making essential pain medicines available, they face a challenging global pharmaceutical market for opioids. Sixty-nine percent of opioids are sold in 4 countries: the United States, Canada, the United Kingdom, and Australia.[5] In comparison, 140 low- and middle-income countries comprise less than 7% of the global opioids market and pharmaceutical companies are often unwilling to invest the time and cost required to register their products in these low-volume countries.

In settings where access to pain relief has been limited for decades, lack of education and experience in pain treatment in the medical community has led to high rates of misunderstanding and misperception and low levels of knowledge and experience.[11,12] Health workers routinely overestimate the risk of side effects and adverse outcomes such as addiction, and are unable to differentiate addiction from physical dependence. Further, they routinely underestimate the effectiveness of opioids and underestimate pain levels in their patients. After years spent practicing medicine in the absence of effective pain relief, many health workers have simply become inured to their patients' suffering, or may not consider pain relief their responsibility. Massive in-service training would be necessary to familiarize health workers with the assessment and treatment of pain and address outdated perceptions and fears.

Just as is observed with other essential medicines, access to pain relief is also limited by weak health systems. For instance, sub-Saharan Africa has 24% of the global burden of disease but only 3% of the global healthcare force,[13] forcing health workers to struggle to treat chronic diseases such as cancer in health systems that were built for acute care, not chronic disease management. Additionally, patients are often unable to access healthcare services because they cannot afford the time or cost of travel to reach them.

RESPONDING TO THE CRISIS

While no single intervention can solve the issue of limited access to pain relief and palliative care, several governments are making steady progress by systematically confronting the barriers described above. This is often done with technical assistance from international non-governmental organizations such as the American Cancer Society, which has a program called Treat the Pain that focuses on improving access to essential pain medicines in resource-limited countries.

In countries where opioids are unavailable, an essential first step is for the ministry of health to assign responsibility to an internal department to improve access to pain relief. For example, the Nigerian Ministry of Health chose the Department of Food and Drug Services; Swaziland selected the National AIDS Program; and Ethiopia, the Medical Services Directorate. The responsible department is then tasked with developing a comprehensive plan to supply and distribute medicines and train health workers on appropriate use. Treat the Pain has collaborated with the ministries of health in these countries to support the addition of technical staff who can focus on expanding access to essential pain medicines.

The introduction of a locally produced

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TREAT THE PAIN™

American Cancer Society® *A program of the American Cancer Society*

Nurse checking patient vitals in Ugandan healthcare facility.

Palliative care is more than just pain relief. Patients with advanced disease also need symptom management, psychosocial support, spiritual support, and assistance with end-of-life issues, including home-based care, legal assistance, and financial assistance.

oral morphine solution was a key breakthrough in sub-Saharan Africa—large-scale local production was pioneered by Hospice Africa Uganda after introducing small-scale production for their patients in the 1990s. The hospice obtains relatively cheap raw morphine powder from the open market, instead of from suppliers who have registered their products in Uganda. The morphine powder can be mixed with water, a preservative, and a colorant in a simple procedure that can be done safely using materials and equipment that can be bought locally. The oral solution has a 6-month shelf life and provides flexible dosing for the treatment of adults and children.

In Uganda, after a prolonged shortage of opioids in the public sector in 2010, the government contracted with Hospice Africa Uganda to produce oral morphine for the whole country, including both the public sector and the private, not-for-profit sector. With some technical assistance from Treat the Pain, Hospice Africa Uganda upgraded its production system to meet the increased demand. The cost of this locally produced oral morphine solution is significantly lower than the cost of imported morphine solution or tablets. Thus, as with other drugs in the essential medicines package, all Ugandan health facilities now have access to free morphine from the government.

Other countries have followed suit, adapting the model to their own situation. For example, the Nigerian Ministry of Health decided to create local morphine production hubs in 25 teaching hospitals around the country, while Swaziland created a central production hub at the national hospital. In Ethiopia, Epharm, a local pharmaceutical company, supplies oral morphine solution to the government.

Once an adequate supply of essential pain medicines has been secured, the next step is distributing the medicines to health facilities and training health workers to assess and treat pain. Coordination of these 2 elements is essential to prevent expiry of unused pain medication on the shelf, as has often been experienced. And if health workers are trained and then return to a work site that does not actually have the medicines available, they rapidly lose the new skills and knowledge and will require retraining.

To address this issue, the Treat the Pain program is partnering with governments in Nigeria, Ethiopia, Uganda, Swaziland, and Kenya to roll out a health worker training program called the Pain-Free Hospital Initiative. The Initiative targets large national referral and teaching hospitals to provide simple, accessible training for physicians, nurses, and pharmacists, to be delivered while staff are in service. The goal of the initiative is to equip staff to assess pain and provide high-quality first-line treatment. In Ethiopia, where morphine has been available only in the oncology department of 1 hospital, the Ministry of Health is implementing the Initiative in 9 hospitals this year while simultaneously making oral morphine available for the first time in those same hospitals. Nigeria is launching it in 4 teaching hospitals, and Swaziland in 12 hospitals.

The provision of high-quality pain relief is a core component of cancer treatment and of palliative care, but palliative care is more than just pain relief. Patients with advanced disease also need symptom management, psychosocial support, spiritual support, and assistance with end-of-life issues, including home-based care, legal assistance, and financial assistance. These services, often modeled on the hospice programs that were created in the United Kingdom and the United States, are often limited in their size and scope, and rely on external donor funding. The challenge going forward will be to integrate these programs into public sector healthcare delivery and create sustainable funding bases for them. **EBO**

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Comprehensive Support for Individuals Living With Prostate Cancer and Their Caregivers Complements Palliative Care Services

Dan Klein; and Jamie Bearse

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INTRODUCTION

ZERO - The End of Prostate Cancer (ZERO) and the Patient Access Network (PAN) Foundation appreciate the opportunity to describe the holistic approach that our organizations use to address the needs of patients with advanced prostate cancer along with the needs of their caregivers and family members. Our unique model shows how 2 nonprofit charitable organizations can join forces to provide a full range of support services which have been shown to help patients and their families. ZERO, which is focused on fostering the first generation without prostate cancer, has the educational resources and support services to help men with prostate cancer, their caregivers, and their loved ones make more informed decisions. The PAN Foundation is an independent patient assistance foundation that provides financial assistance to underinsured patients who enroll in its castrate-resistant prostate cancer (CRPC) assistance program—1 of nearly 60 disease-specific cost-sharing programs offered by the PAN Foundation.[1] Combined with palliative and supportive care, this comprehensive approach improves the prostate cancer journey for many patients.

WHAT IS PALLIATIVE CARE?

The National Cancer Institute defines palliative care as "care given to improve the quality of life of patients who have a serious or life-threatening disease, such as cancer."[2] Initiated at the time of diagnosis and extending throughout the course of illness, palliative care is usually provided by a specialist who may be a doctor working with a multidisciplinary team of healthcare professionals, such as other specialist doctors, nurses, registered dieticians, pharmacists, and social workers, who address the emotional, physical, practical, and spiritual issues of the patient and family members as needed.[2]

PROSTATE CANCER PATIENTS BENEFIT FROM PARTNERSHIP BETWEEN 2 NATIONAL NONPROFIT ORGANIZATIONS

ZERO provides education and support to men and their families diagnosed with prostate cancer, regardless of stage. Aware of the overwhelming and frightening impact of a cancer diagnosis, ZERO provides newly diagnosed men with information on prostate cancer, including treatment options, with the objective of making them comfortable discussing their disease with their doctor and ultimately making treatment decisions. ZERO's support extends throughout the prostate cancer journey.

Recognizing that some of these men are underinsured and in need of financial assistance to cover the cost-sharing amounts required by Medicare and private insurers, ZERO partnered with the PAN Foundation, which has a CRPC copay assistance program for underinsured patients with income less than 500% of the Federal Poverty Level (approximately $59,000 for an individual or almost $80,000 for a couple).[3]

Together, ZERO and PAN offer educational and financial support for men and their caregivers at different points along the prostate cancer journey. In addition to assisting patients with becoming better informed, the educational resources of ZERO help patients cope with life following treatment. The financial assistance provided by the PAN Foundation to men who are refractory to hormone therapy removes the barrier of unaffordable cost-sharing amounts that prevents them from accessing critical therapies.

The comprehensive approach offered by ZERO and PAN for prostate cancer includes the key elements that improve patient outcomes. For example, researchers have demonstrated that an informed patient, who can discuss the pros and cons of treatment options with his doctor, can have a positive impact on the quality of care and outcomes.[4] Similarly, eliminating financial barriers such as cost-sharing amounts for specialty drugs improves patient adherence to treatment regimens.[5]

The harsh reality for many people today is that they may not be able to afford the treatment and cures that modern medicine has made possible unless they receive help from charitable co-payment foundations. The collaboration between ZERO and the PAN Foundation represents an ideal model that can be adopted by other nonprofit patient organizations and patient financial assistance foundations to provide comprehensive services and support to complement the professional services provided by a palliative care team.

The harsh reality for many people today is that they may not be able to afford the treatment and cures that modern medicine has made possible unless they receive help from charitable co-payment foundations.

COMPLEMENTING PALLIATIVE CARE SERVICES

ZERO helps patients and caregivers navigate the journey that begins with the diagnosis of prostate cancer. Understanding that patients may feel unprepared, anxious, or overwhelmed after learning they have prostate cancer, ZERO provides resources and services tailored to meet the unique needs of patients and their caregivers. Specifically, ZERO emphasizes the importance of learning the "language of prostate cancer," including terminology associated with types of diagnostic tests; tumor characteristics; and the appropriate treatment options available based on the stage, grade, and risk category of the individual's prostate cancer. This knowledge will embolden patients and their caregivers to ask appropriate questions about the diagnosis and treatment options as they choose a healthcare team to support the journey.

Choosing a Healthcare Team

ZERO reminds men with newly diagnosed prostate cancer that they have a choice of who manages their care. ZERO's educational resources emphasize the need for a patient to find a team they trust with making decisions that align with their best interests and preferences.

Most men learn they have prostate cancer from a urologist, who typically has been involved with confirming the diagnosis, either through biopsy or imaging. Urologists, many of whom perform prostate cancer surgery and some of whom have oncology and/or radiology training, play a major role in managing the care of patients with prostate cancer, including surgery, radiation therapy, hormonal therapy, treatment of advanced disease, clinical trials, and active surveillance.

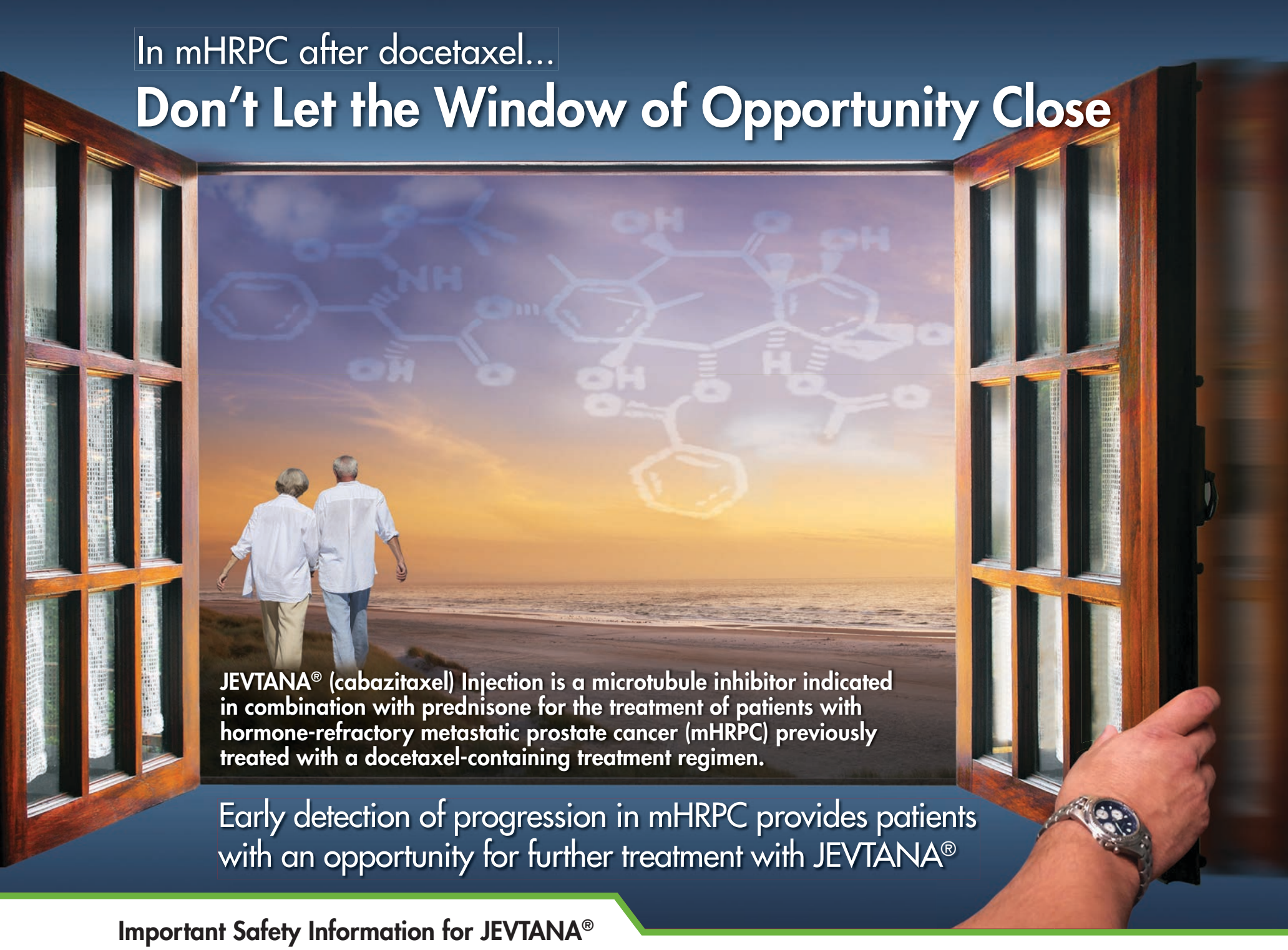
Value of a Multidisciplinary Approach

Recognizing the range of emotional, physical, and practical issues associated with cancer diagnosis and treatment, ZERO encourages men to consider seeking help from a multidisciplinary medical team. Composed of healthcare professionals from different specialties, members of a multidisciplinary team work together to suggest a treatment plan based on an individual's diagnosis, health history, and preferences, factors

(continued on page **SP207**)

In mHRPC after docetaxel…

Don’t Let the Window of Opportunity Close



JEVTANA® (cabazitaxel) Injection is a microtubule inhibitor indicated in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer (mHRPC) previously treated with a docetaxel-containing treatment regimen.

Early detection of progression in mHRPC provides patients with an opportunity for further treatment with JEVTANA®

Important Safety Information for JEVTANA®

WARNING: NEUTROPENIA AND HYPERSENSITIVITY

- **Neutropenic deaths have been reported. In order to monitor the occurrence of neutropenia, frequent blood cell counts should be performed on all patients receiving JEVTANA®. JEVTANA® should not be given to patients with neutrophil counts of ≤1,500 cells/mm^3**
- **Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of the JEVTANA® infusion and administration of appropriate therapy. Patients should receive premedication**
- **JEVTANA® must not be given to patients who have a history of severe hypersensitivity reactions to JEVTANA® or to other drugs formulated with polysorbate 80**

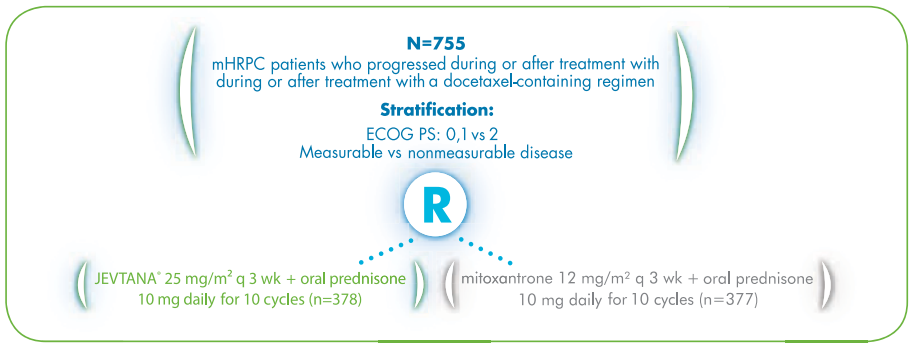
Please see additional Important Safety Information and Brief Summary of Full Prescribing Information, including boxed WARNINGS, on adjacent pages.

JEVTANA®
(cabazitaxel)
Injection

In mHRPC after docetaxel…

Include the Proven Benefits With JEVTANA® (cabazitaxel) Injection In Your Treatment Plan for mHRPC

JEVTANA® validated in TROPIC: A landmark phase III trial in second-line mHRPC[1,2]



Endpoints[3]

- Primary endpoint: OS
- Secondary endpoints: Investigator-assessed tumor response,* safety, pharmacokinetics

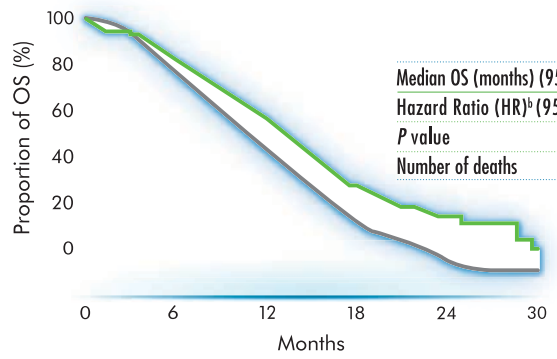
*For measurable disease according to RECIST criteria.
RECIST=Response Evaluation Criteria In Solid Tumors.

Large, international, randomized, open-label registration study (N=755)[1,2]

- Enrolled patients with mHRPC who progressed on or after docetaxel
- Controlled versus an active agent: mitoxantrone
- Open-label: Conducted in 146 sites in 26 countries

JEVTANA® provides a significant OS benefit and improved tumor response after docetaxel, validating this taxane-to-taxane treatment strategy in mHRPC[1]

TROPIC: OS[a] versus mitoxantrone + prednisone[2]



	JEVTANA® + prednisone n=378	mitoxantrone + prednisone n=377
Median OS (months) (95% CI)	15.1 (14.1–16.3)	12.7 (11.6–13.7)
Hazard Ratio (HR)[b] (95% CI)	0.70 (0.59–0.83)	
P value	<.0001	
Number of deaths	234 (62%)	279 (74%)

[a] Primary endpoint.
[b] HR estimated using COX model; an HR of <1 favors JEVTANA®.

- **15.1 months (95% CI: 14.1–16.3) median OS** versus 12.7 months (95% CI: 11.6–13.7) with mitoxantrone (*P*<.0001)[1]
- **30% reduced risk of death** versus mitoxantrone (HR=0.70)[1]
- **14.4% (95% CI: 9.6–19.3) investigator-assessed tumor response** versus 4.4% (95% CI:1.6–7.2) with mitoxantrone (*P*=.0005)[1]
- No overall differences in effectiveness were observed between patients ≥65 years of age and younger patients[1]

Important Safety Information for JEVTANA®

- Patients ≥65 years of age were more likely to experience fatal outcomes not related to disease progression and certain adverse reactions, including neutropenia and febrile neutropenia. Monitor closely
- Deaths due to causes other than disease progression within 30 days of last study drug dose were reported in 18 (5%) JEVTANA®-treated patients. The most common fatal adverse reactions in JEVTANA®-treated patients were infections (n=5) and renal failure (n=4)
- The majority (4 of 5 patients) of fatal infection-related adverse reactions occurred after a single dose of JEVTANA®. Other fatal adverse reactions in JEVTANA®-treated patients included ventricular fibrillation, cerebral hemorrhage, and dyspnea

JEVTANA® (cabazitaxel) Injection Select Safety Information

Summary of hematologic AEs[1]

Hematologic AEs ≥5%	JEVTANA® 25 mg/m² q 3 wk + prednisone 10 mg qd (n=371)		mitoxantrone 12 mg/m² q 3 wk + prednisone 10 mg qd (n=371)	
	Grade 1–4, n (%)	Grade 3–4, n (%)	Grade 1–4, n (%)	Grade 3–4, n (%)
Neutropenia[a]	347 (94%)	303 (82%)	325 (87%)	215 (58%)
Febrile neutropenia	27 (7%)	27 (7%)	5 (1%)	5 (1%)
Anemia[a]	361 (98%)	39 (11%)	302 (82%)	18 (5%)
Leukopenia[a]	355 (96%)	253 (69%)	343 (93%)	157 (42%)
Thrombocytopenia[a]	176 (48%)	15 (4%)	160 (43%)	6 (2%)

[a] Based on laboratory values: JEVTANA® (n=369), mitoxantrone (n=370).

- Protocol did not permit primary prophylaxis with granulocyte colony-stimulating factor at cycle 1[2]
- Treatment discontinuations due to adverse drug reactions occurred in 18% of patients who received JEVTANA® and 8% of patients who received mitoxantrone

Safety evaluation of fatal adverse reactions (ARs)[1]

- Deaths due to causes other than disease progression*
  - 5% (18/371) of JEVTANA®-treated patients
  - <1% (3/371) of mitoxantrone-treated patients
- Most common fatal ARs in JEVTANA®-treated patients
  - Infections: sepsis or septic shock (n=5)
    - All had grade 4 neutropenia; 1 had febrile neutropenia
    - 4 of 5 occurred after a single dose of JEVTANA®
  - Renal failure (n=4)
- Other fatal ARs in JEVTANA®-treated patients
  - Ventricular fibrillation
  - Cerebral hemorrhage
  - Dyspnea

*Within 30 days of last study drug dose.

JEVTANA® is a microtubule inhibitor indicated in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer (mHRPC) previously treated with a docetaxel-containing treatment regimen.

Please see additional Important Safety Information and Brief Summary of Full Prescribing Information, including boxed WARNINGS, on adjacent pages.

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JEVTANA® (cabazitaxel) Injection

Important Safety Information for JEVTANA® (cabazitaxel) Injection

WARNING: NEUTROPENIA AND HYPERSENSITIVITY

- **Neutropenic deaths have been reported. In order to monitor the occurrence of neutropenia, frequent blood cell counts should be performed on all patients receiving JEVTANA®. JEVTANA® should not be given to patients with neutrophil counts of ≤1,500 cells/mm^3**
- **Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of the JEVTANA® infusion and administration of appropriate therapy. Patients should receive premedication**
- **JEVTANA® must not be given to patients who have a history of severe hypersensitivity reactions to JEVTANA® or to other drugs formulated with polysorbate 80**

CONTRAINDICATIONS

- JEVTANA® should not be used in patients with neutrophil counts of ≤1,500/mm^3
- JEVTANA® is contraindicated in patients who have a history of severe hypersensitivity reactions to JEVTANA® or to other drugs formulated with polysorbate 80

WARNINGS AND PRECAUTIONS

- Neutropenic deaths have been reported
  - Monitoring of complete blood counts is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed
  - Monitor blood counts frequently to determine if initiation of G-CSF and/or dosage modification is needed
  - Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features
- Severe hypersensitivity reactions can occur
  - Premedicate with antihistamines, corticosteroids and H_2 antagonists
  - Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions
  - Discontinue infusion immediately if hypersensitivity is observed and treat as indicated
- Mortality related to diarrhea has been reported
  - Rehydrate and treat with anti-emetics and anti-diarrheals as needed
  - If experiencing grade ≥3 diarrhea, dosage should be modified
- Nausea, vomiting and severe diarrhea, at times, may occur. Death related to diarrhea and electrolyte imbalance occurred in the randomized clinical trial. Intensive measures may be required for severe diarrhea and electrolyte imbalance
- Gastrointestinal (GI) hemorrhage and perforation, ileus, enterocolitis, neutropenic enterocolitis, including fatal outcome, have been reported
  - Risk may be increased with neutropenia, age, steroid use, concomitant use of NSAIDs, anti-platelet therapy or anti-coagulants, and prior history of pelvic radiotherapy, adhesions, ulceration and GI bleeding
  - Abdominal pain and tenderness, fever, persistent constipation, diarrhea, with or without neutropenia, may be early manifestations of serious GI toxicity and should be evaluated and treated promptly
  - JEVTANA® treatment delay or discontinuation may be necessary
- Renal failure, including cases with fatal outcomes, has been reported. Identify cause and manage aggressively
- Patients ≥65 years of age were more likely to experience fatal outcomes not related to disease progression and certain adverse reactions, including neutropenia and febrile neutropenia. Monitor closely
- Patients with impaired hepatic function were excluded from the randomized clinical trial
  - Hepatic impairment is likely to increase the JEVTANA® concentrations
  - JEVTANA® should not be given to patients with hepatic impairment
- JEVTANA® can cause fetal harm when administered to a pregnant woman
  - There are no adequate and well-controlled studies in pregnant women using JEVTANA®
  - Women of childbearing potential should be advised to avoid becoming pregnant during treatment with JEVTANA®

ADVERSE REACTIONS

- Deaths due to causes other than disease progression within 30 days of last study drug dose were reported in 18 (5%) JEVTANA®-treated patients. The most common fatal adverse reactions in JEVTANA®-treated patients were infections (n=5) and renal failure (n=4)
- The most common (≥10%) grade 1–4 adverse reactions were anemia, leukopenia, neutropenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia
- The most common (≥5%) grade 3–4 adverse reactions in patients who received JEVTANA® were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia

Please see Brief Summary of Full Prescribing Information, including boxed WARNINGS, on adjacent pages.

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SANOFI ONCOLOGY

JEVTANA® (cabazitaxel) Injection

JEVTANA® **Rx Only**
(cabazitaxel) Injection, 60 mg/1.5 mL, for intravenous infusion only

Brief Summary of Prescribing Information

WARNING : NEUTROPENIA AND HYPERSENSITIVITY

Neutropenic deaths have been reported. In order to monitor the occurrence of neutropenia, frequent blood cell counts should be performed on all patients receiving JEVTANA. JEVTANA should not be given to patients with neutrophil counts of ≤1,500 cells/mm^3.

Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of the JEVTANA infusion and administration of appropriate therapy *[see Warnings and Precautions (5.2)]*. Patients should receive premedication *[see Dosage and Administrations (2.3)]*. JEVTANA must not be given to patients who have a history of severe hypersensitivity reactions to JEVTANA or to other drugs formulated with polysorbate 80 *[see Contraindications (4)]*.

1. INDICATIONS AND USAGE

JEVTANA® is a microtubule inhibitor indicated in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

2. DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

- The individual dosage of JEVTANA is based on calculation of the Body Surface Area (BSA) and is 25 mg/m^2 administered as a one-hour intravenous infusion every three weeks in combination with oral prednisone 10 mg administered daily throughout JEVTANA treatment.
- Premedication is recommended prior to treatment *[see Dosage and Administration (2.3)]*.
- JEVTANA should be administered under the supervision of a qualified physician experienced in the use of antineoplastic medicinal products. Appropriate management of complications is possible only when the adequate diagnostic and treatment facilities are readily available.
- JEVTANA Injection single-use vial requires **two** dilutions prior to administration *[see Dosage and Administration (2.5)]*.
- Do not use PVC infusion containers and polyurethane infusions sets for preparation and administration of JEVTANA infusion solution *[see Dosage and Administration (2.5)]*.
- Both the JEVTANA Injection and the diluent vials contain an overfill to compensate for liquid loss during preparation.

2.2 Dose Modifications for Adverse Reactions

The JEVTANA dose should be reduced if patients experience the following adverse reactions.

Table 1: Recommended Dosage Modifications for Adverse Reactions in Patients Treated with JEVTANA

Toxicity	Dosage Modification
Prolonged grade ≥ 3 neutropenia (greater than 1 week) despite appropriate medication including G-CSF	Delay treatment until neutrophil count is > 1,500 cells/mm^3, then reduce dosage of JEVTANA to 20 mg/m^2. Use G-CSF for secondary prophylaxis.
Febrile neutropenia or neutropenic infection	Delay treatment until improvement or resolution, and until neutrophil count is > 1,500 cells/mm^3, then reduce dosage of JEVTANA to 20 mg/m^2. Use G-CSF for secondary prophylaxis.
Grade ≥ 3 diarrhea or persisting diarrhea despite appropriate medication, fluid and electrolytes replacement	Delay treatment until improvement or resolution, then reduce dosage of JEVTANA to 20 mg/m^2.
Grade 2 peripheral neuropathy	Delay treatment until improvement or resolution, then reduce dosage of JEVTANA to 20 mg/m^2.
Grade ≥3 peripheral neuropathy	Discontinue JEVTANA

Discontinue JEVTANA treatment if a patient continues to experience any of these reactions at 20 mg/m^2.

2.3 Dose Modifications for Drug Interactions

Strong CYP3A inhibitors

Concomitant drugs that are strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase plasma concentrations of cabazitaxel. Avoid the coadministration of JEVTANA with these drugs. If patients require co-administration of a strong CYP3A inhibitor, consider a 25% JEVTANA dose reduction *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3) in the full prescribing information]*.

2.4 Premedication

Premedicate at least 30 minutes prior to each dose of JEVTANA with the following intravenous medications to reduce the risk and/or severity of hypersensitivity:

- antihistamine (dexchlorpheniramine 5 mg, or diphenhydramine 25 mg or equivalent antihistamine),
- corticosteroid (dexamethasone 8 mg or equivalent steroid),
- H_2 antagonist (ranitidine 50 mg or equivalent H_2 antagonist).

Antiemetic prophylaxis is recommended and can be given orally or intravenously as needed.

2.5 Administration Precautions

JEVTANA is a cytotoxic anticancer drug and caution should be exercised when handling and preparing JEVTANA solutions, taking into account the use of containment devices, personal protective equipment (e.g., gloves), and preparation procedures. Please refer to *Handling and Disposal (16.3) in the full prescribing information.*

If JEVTANA Injection, first diluted solution, or second (final) dilution for intravenous infusion should come into contact with the skin, immediately and thoroughly wash with soap and water.

If JEVTANA Injection, first diluted solution, or second (final) dilution for intravenous infusion should come into contact with mucosa, immediately and thoroughly wash with water.

2.6 Instructions for Preparation

Do not use PVC infusion containers or polyurethane infusions sets for preparation and administration of JEVTANA infusion solution.

Read this **entire** section carefully before mixing and diluting. JEVTANA requires **two** dilutions prior to administration. Please follow the preparation instructions provided below, as improper preparation may lead to overdose *[see Overdosage (10)]*.

Note: Both the JEVTANA Injection and the diluent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the **entire contents** of the accompanying diluent, there is an initial diluted solution containing 10 mg/mL JEVTANA. The following two-step dilution process must be carried out under aseptic conditions to prepare the second (final) infusion solution.

Inspect the JEVTANA Injection and supplied diluent vials. The JEVTANA Injection is a clear yellow to brownish-yellow viscous solution.

Step 1 – First Dilution

Each vial of JEVTANA (cabazitaxel) 60 mg/1.5 mL must first be mixed with the **entire contents** of supplied diluent. Once reconstituted, the resultant solution contains 10 mg/mL of JEVTANA. When transferring the diluent, direct the needle onto the inside wall of JEVTANA vial and inject slowly to limit foaming. Remove the syringe and needle and gently mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixing of the drug and diluent. Do not shake.

Let the solution stand for a few minutes to allow any foam to dissipate, and check that the solution is homogeneous and contains no visible particulate matter. It is not required that all foam dissipate prior to continuing the preparation process.

The resulting initial diluted JEVTANA solution (cabazitaxel 10 mg/mL) requires further dilution before administration. The second dilution should be done immediately (within 30 minutes) to obtain the final infusion as detailed in Step 2.

Step 2 – Second (Final) Dilution

Withdraw the recommended dose from the JEVTANA solution containing 10 mg/mL as prepared in Step 1 using a calibrated syringe and further dilute into a sterile 250 mL PVC-free container of either 0.9% sodium chloride solution or 5% dextrose solution for infusion. If a dose greater than 65 mg of JEVTANA is required, use a larger volume of the infusion vehicle so that a concentration of 0.26 mg/mL JEVTANA is not exceeded. The concentration of the JEVTANA final infusion solution should be between 0.10 mg/mL and 0.26 mg/mL.

JEVTANA should not be mixed with any other drugs.

Remove the syringe and thoroughly mix the final infusion solution by gently inverting the bag or bottle.

JEVTANA final infusion solution (in either 0.9% sodium chloride solution or 5% dextrose solution) should be used within 8 hours at ambient temperature (including the one-hour infusion) or within a total of 24 hours if refrigerated (including the one-hour infusion).

As the final infusion solution is supersaturated, it may crystallize over time. Do not use if this occurs and discard.

Inspect visually for particulate matter, any crystals and discoloration prior to administration. If the JEVTANA first diluted solution or second (final) infusion solution is not clear or appears to have precipitation, it should be discarded.

Discard any unused portion.

2.7 Administration

The final JEVTANA infusion solution should be administered intravenously as a one-hour infusion at room temperature.

Use an in-line filter of 0.22 micrometer nominal pore size (also referred to as 0.2 micrometer) during administration.

The final JEVTANA infusion solution should be used immediately. However, in-use storage time can be longer under specific conditions, i.e. 8 hours under ambient conditions (including the one-hour infusion) or for a total of 24 hours if refrigerated (including the one-hour infusion) *[see Dosage and Administration (2.5)]*.

4. CONTRAINDICATIONS

JEVTANA should not be used in patients with neutrophil counts of ≤ 1,500/mm^3.

JEVTANA is contraindicated in patients who have a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80.

5. WARNINGS AND PRECAUTIONS

5.1 Neutropenia

Five patients experienced fatal infectious adverse events (sepsis or septic shock). All had grade 4 neutropenia and one had febrile neutropenia. One additional patient's death was attributed to neutropenia without a documented infection.

G-CSF may be administered to reduce the risks of neutropenia complications associated with JEVTANA use. Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features (age > 65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia. Therapeutic use of G-CSF and secondary prophylaxis should be considered in all patients considered to be at increased risk for neutropenia complications.

Monitoring of complete blood counts is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed *[see Dosage and Administration (2.2)]*.

JEVTANA should not be administered to patients with neutrophils ≤ 1,500/mm^3 *[see Contraindications (4)]*.

If a patient experiences febrile neutropenia or prolonged neutropenia (greater than one week) despite appropriate medication (e.g., G-CSF), the dose of JEVTANA should be reduced *[see Dosage and Administration (2.2)]*. Patients can restart treatment with JEVTANA only when neutrophil counts recover to a level > 1,500/mm^3 *[see Contraindications (4)]*.

5.2 Hypersensitivity Reactions

All patients should be premedicated prior to the initiation of the infusion of JEVTANA *[see Dosage and Administration (2.4)]*. Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of JEVTANA, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available. Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of the JEVTANA infusion and appropriate therapy. Patients with a history of severe hypersensitivity reactions should not be re-challenged with JEVTANA *[see Contraindications (4)]*.

5.3 Gastrointestinal Disorders

Nausea, vomiting and severe diarrhea, at times, may occur. Death related to diarrhea and electrolyte imbalance occurred in the randomized clinical trial. Intensive measures may be required for severe diarrhea and electrolyte imbalance. Patients should be treated with rehydration, anti-diarrheal or anti-emetic medications as needed. Treatment delay or dosage reduction may be necessary if patients experience Grade ≥ 3 diarrhea *[see Dosage and Administration (2.2)]*.

Gastrointestinal (GI) hemorrhage and perforation, ileus, enterocolitis, neutropenic enterocolitis, including fatal outcome, have been reported in patients treated with JEVTANA *[see Adverse Reactions (6.2)]*. Risk may be increased with neutropenia, age, steroid use, concomitant use of NSAIDs, anti-platelet therapy or anti-coagulants, and patients with a prior history of pelvic radiotherapy, adhesions, ulceration and GI bleeding.

Abdominal pain and tenderness, fever, persistent constipation, diarrhea, with or without neutropenia, may be early manifestations of serious gastrointestinal toxicity and should be evaluated and treated promptly. JEVTANA treatment delay or discontinuation may be necessary.

5.4 Renal Failure

Renal failure, including four cases with fatal outcome, was reported in the randomized clinical trial. Most cases occurred in association with sepsis, dehydration, or obstructive uropathy *[see Adverse Reactions (6.1)]*. Some deaths due to renal failure did not have a clear etiology. Appropriate measures should be taken to identify causes of renal failure and treat aggressively.

5.5 Elderly Patients

In the randomized clinical trial, 3 of 131 (2%) patients < 65 years of age and 15 of 240 (6%) ≥ 65 years of age died of causes other than disease progression within 30 days of the last cabazitaxel dose. Patients ≥ 65 years of age are more likely to experience certain adverse reactions, including neutropenia and febrile neutropenia *[see Adverse Reactions (6) and Use in Specific Populations (8.5)]*.

5.6 Hepatic Impairment

No dedicated hepatic impairment trial for JEVTANA has been conducted. Patients with impaired hepatic function (total bilirubin ≥ ULN, or AST and/or ALT ≥ 1.5 x ULN) were excluded from the randomized clinical trial.

Cabazitaxel is extensively metabolized in the liver, and hepatic impairment is likely to increase cabazitaxel concentrations.

Hepatic impairment increases the risk of severe and life-threatening complications in patients receiving other drugs belonging to the same class as JEVTANA. JEVTANA should not be given to patients with hepatic impairment (total bilirubin ≥ ULN, or AST and/or ALT ≥ 1.5 x ULN).

5.7 Pregnancy

Pregnancy category D.

JEVTANA can cause fetal harm when administered to a pregnant woman. In non-clinical studies in rats and rabbits, cabazitaxel was embryotoxic, fetotoxic, and abortifacient at exposures significantly lower than those expected at the recommended human dose level.

There are no adequate and well-controlled studies in pregnant women using JEVTANA. 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 the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during treatment with JEVTANA *[see Use in Specific Populations (8.1)]*.

6. ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Neutropenia *[see Warnings and Precautions (5.1)]*.
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*.
- Gastrointestinal Disorders *[see Warnings and Precautions (5.3)]*.
- Renal Failure *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trial Experience

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

The safety of JEVTANA in combination with prednisone was evaluated in 371 patients with hormone-refractory metastatic prostate cancer treated in a single randomized trial, compared to mitoxantrone plus prednisone.

Deaths due to causes other than disease progression within 30 days of last study drug dose were reported in 18 (5%) JEVTANA-treated patients and 3 (< 1%) mitoxantrone-treated patients. The most common fatal adverse reactions in JEVTANA-treated patients were infections (n=5) and renal failure (n=4). The majority (4 of 5 patients) of fatal infection-related adverse reactions occurred after a single dose of JEVTANA. Other fatal adverse reactions in JEVTANA-treated patients included ventricular fibrillation, cerebral hemorrhage, and dyspnea.

The most common (≥ 10%) grade 1–4 adverse reactions were anemia, leukopenia, neutropenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysguesia, cough, arthralgia, and alopecia.

The most common (≥ 5%) grade 3–4 adverse reactions in patients who received JEVTANA were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia.

Treatment discontinuations due to adverse drug reactions occurred in 18% of patients who received JEVTANA and 8% of patients who received mitoxantrone. The most common adverse reactions leading to treatment discontinuation in the JEVTANA group were neutropenia and renal failure. Dose reductions were reported in 12% of JEVTANA-treated patients and 4% of mitoxantrone-treated patients. Dose delays were reported in 28% of JEVTANA-treated patients and 15% of mitoxantrone-treated patients.

Table 2 – Incidence of Reported Adverse Reactions* and Hematologic Abnormalities in ≥ 5% of Patients Receiving JEVTANA in Combination with Prednisone or Mitoxantrone in Combination with Prednisone

	JEVTANA 25 mg/m^2 every 3 weeks with prednisone 10 mg daily n=371		Mitoxantrone 12 mg/m^2 every 3 weeks with prednisone 10 mg daily n=371	
	Grade 1–4 n (%)	Grade 3–4 n (%)	Grade 1–4 n (%)	Grade 3–4 n (%)
Any Adverse Reaction				
Blood and Lymphatic System Disorders				
Neutropenia†	347 (94%)	303 (82%)	325 (87%)	215 (58%)
Febrile Neutropenia	27 (7%)	27 (7%)	5 (1%)	5 (1%)
Anemia†	361 (98%)	39 (11%)	302 (82%)	18 (5%)
Leukopenia†	355 (96%)	253 (69%)	343 (93%)	157 (42%)
Thrombocytopenia†	176 (48%)	15 (4%)	160 (43%)	6 (2%)
Cardiac Disorders				
Arrhythmia‡	18 (5%)	4 (1%)	6 (2%)	1 (< 1%)
Gastrointestinal Disorders				
Diarrhea	173 (47%)	23 (6%)	39 (11%)	1 (< 1%)
Nausea	127 (34%)	7 (2%)	85 (23%)	1 (< 1%)
Vomiting	83 (22%)	6 (2%)	38 (10%)	0
Constipation	76 (20%)	4 (1%)	57 (15%)	2 (< 1%)
Abdominal Pain§	64 (17%)	7 (2%)	23 (6%)	0
Dyspepsia¶	36 (10%)	0	9 (2%)	0
General Disorders and Administration Site Conditions				
Fatigue	136 (37%)	18 (5%)	102 (27%)	11 (3%)
Asthenia	76 (20%)	17 (5%)	46 (12%)	9 (2%)
Pyrexia	45 (12%)	4 (1%)	23 (6%)	1 (< 1%)
Peripheral Edema	34 (9%)	2 (< 1%)	34 (9%)	2 (< 1%)
Mucosal Inflammation	22 (6%)	1 (< 1%)	10 (3%)	1 (< 1%)
Pain	20 (5%)	4 (1%)	18 (5%)	7 (2%)
Infections and Infestations				
Urinary Tract Infection#	29 (8%)	6 (2%)	12 (3%)	4 (1%)
Investigations				
Weight Decreased	32 (9%)	0	28 (8%)	1 (< 1%)
Metabolism and Nutrition Disorders				
Anorexia	59 (16%)	3 (< 1%)	39 (11%)	3 (< 1%)
Dehydration	18 (5%)	8 (2%)	10 (3%)	3 (< 1%)
Musculoskeletal and Connective Tissue Disorders				
Back Pain	60 (16%)	14 (4%)	45 (12%)	11 (3%)
Arthralgia	39 (11%)	4 (1%)	31 (8%)	4 (1%)
Muscle Spasms	27 (7%)	0	10 (3%)	0
Nervous System Disorders				
Peripheral Neuropathy▷	50 (13%)	3 (< 1%)	12 (3.2%)	3 (< 1%)
Dysgeusia	41 (11%)	0	15 (4%)	0
Dizziness	30 (8%)	0	21 (6%)	2 (< 1%)
Headache	28 (8%)	0	19 (5%)	0
Renal and Urinary Tract Disorders				
Hematuria	62 (17%)	7 (2%)	13 (4%)	1 (< 1%)
Dysuria	25 (7%)	0	5 (1%)	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	43 (12%)	4 (1%)	16 (4%)	2 (< 1%)
Cough	40 (11%)	0	22 (6%)	0

Table 2 – Incidence of Reported Adverse Reactions* and Hematologic Abnormalities in ≥ 5% of Patients Receiving JEVTANA in Combination with Prednisone or Mitoxantrone in Combination with Prednisone (continued)

	JEVTANA 25 mg/m² every 3 weeks with prednisone 10 mg daily n=371		Mitoxantrone 12 mg/m² every 3 weeks with prednisone 10 mg daily n=371	
	Grade 1–4 n (%)	Grade 3–4 n (%)	Grade 1–4 n (%)	Grade 3–4 n (%)
Skin and Subcutaneous Tissue Disorders				
Alopecia	37 (10%)	0	18 (5%)	0
Vascular Disorders				
Hypotension	20 (5%)	2 (<1 %)	9 (2%)	1 (< 1%)
Median Duration of Treatment	6 cycles		4 cycles	

*Graded using NCI CTCAE version 3

†Based on laboratory values, cabazitaxel: n =369, mitoxantrone: n = 370.

‡Includes atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block complete, bradycardia, palpitations, supraventricular tachycardia, tachyarrhythmia, and tachycardia.

§Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.

¶Includes gastroesophageal reflux disease and reflux gastritis.

#Includes urinary tract infection enterococcal and urinary tract infection fungal.

ÞIncludes peripheral motor neuropathy and peripheral sensory neuropathy.

Neutropenia and Associated Clinical Events:

Five patients experienced fatal infectious adverse events (sepsis or septic shock). All had grade 4 neutropenia and one had febrile neutropenia. One additional patient's death was attributed to neutropenia without a documented infection. Twenty-two (6%) patients discontinued JEVTANA treatment due to neutropenia, febrile neutropenia, infection, or sepsis. The most common adverse reaction leading to treatment discontinuation in the JEVTANA group was neutropenia (2%).

Hematuria:

Adverse events of hematuria, including those requiring medical intervention, were more common in JEVTANA-treated patients. The incidence of grade ≥ 2 hematuria was 6% in JEVTANA-treated patients and 2% in mitoxantrone-treated patients. Other factors associated with hematuria were well-balanced between arms and do not account for the increased rate of hematuria on the JEVTANA arm.

Hepatic Laboratory Abnormalities:

The incidences of grade 3–4 increased AST, increased ALT, and increased bilirubin were each ≤ 1%.

Elderly Population:

The following grade 1–4 adverse reactions were reported at rates ≥ 5% higher in patients 65 years of age or greater compared to younger patients: fatigue (40% vs. 30%), neutropenia (97% vs. 89%), asthenia (24% vs. 15%), pyrexia (15% vs. 8%), dizziness (10% vs. 5%), urinary tract infection (10% vs. 3%) and dehydration (7% vs. 2%), respectively.

The incidence of the following grade 3–4 adverse reactions were higher in patients ≥ 65 years of age compared to younger patients; neutropenia (87% vs. 74%), and febrile neutropenia (8% vs. 6%) *[see Use in Specific Populations (8.5)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified from clinical trials and/or post-marketing surveillance. Because they are reported from a population of unknown size, precise estimates of frequency cannot be made.

Gastrointestinal: Gastritis, intestinal obstruction.

7. DRUG INTERACTIONS

7.1 Drugs That May Increase Cabazitaxel Plasma Concentrations

CYP3A4 Inhibitors: Cabazitaxel is primarily metabolized through CYP3A *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase plasma concentrations of cabazitaxel. Avoid the co-administration of JEVTANA with strong CYP3A inhibitors. If patients require co-administration of a strong CYP3A inhibitor, consider a 25% JEVTANA dose reduction *[see Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3) in the full prescribing information]*.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy category D. See 'Warnings and Precautions' section.

JEVTANA can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of JEVTANA in pregnant women.

Non-clinical studies in rats and rabbits have shown that cabazitaxel is embryotoxic, fetotoxic, and abortifacient. Cabazitaxel was shown to cross the placenta barrier within 24 hours of a single intravenous administration of a 0.08 mg/kg dose (approximately 0.02 times the maximum recommended human dose-MRHD) to pregnant rats at gestational day 17.

Cabazitaxel administered once daily to female rats during organogenesis at a dose of 0.16 mg/kg/day (approximately 0.02–0.06 times the Cmax in patients with cancer at the recommended human dose) caused maternal and embryofetal toxicity consisting of increased post-implantation loss, embryolethality, and fetal deaths. Decreased mean fetal birth weight associated with delays in skeletal ossification were observed at doses ≥ 0.08 mg/kg (approximately 0.02 times the Cmax at the MRHD). *In utero* exposure to cabazitaxel did not result in fetal abnormalities in rats or rabbits at exposure levels significantly lower than the expected human exposures.

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 the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while taking JEVTANA.

8.3 Nursing Mothers

Cabazitaxel or cabazitaxel metabolites are excreted in maternal milk of lactating rats. It is not known whether this drug is excreted in human milk. Within 2 hours of a single intravenous administration of cabazitaxel to lactating rats at a dose of 0.08 mg/kg (approximately 0.02 times the maximum recommended human dose), radioactivity related to cabazitaxel was detected in the stomachs of nursing pups. This was detectable for up to 24 hours post-dose. Approximately 1.5% of the dose delivered to the mother was calculated to be delivered in the maternal milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from JEVTANA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

Based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of cabazitaxel between patients < 65 years (n=100) and older (n=70).

Of the 371 patients with prostate cancer treated with JEVTANA every three weeks plus prednisone, 240 patients (64.7%) were 65 years of age and over, while 70 patients (18.9%) were 75 years of age and over. No overall differences in effectiveness were observed between patients ≥ 65 years of age and younger patients. Elderly patients (≥ 65 years of age) may be more likely to experience certain adverse reactions. The incidence of neutropenia, fatigue, asthenia, pyrexia, dizziness, urinary tract infection and dehydration occurred at rates ≥ 5% higher in patients who were 65 years of age or greater compared to younger patients *[see Adverse Reactions (6.1)]*.

8.6 Renal Impairment

No dedicated renal impairment trial for JEVTANA has been conducted. Based on the population pharmacokinetic analysis, no significant difference in clearance was observed in patients with mild (50 mL/min ≤ creatinine clearance (CLcr) < 80 mL/min) and moderate renal impairment (30 mL/min ≤ CLcr < 50 mL/min). No data are available for patients with severe renal impairment or end-stage renal disease *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Caution should be used in patients with severe renal impairment (CLcr < 30 mL/min) and patients with end-stage renal diseases.

8.7 Hepatic Impairment

No dedicated hepatic impairment trial for JEVTANA has been conducted. The safety of JEVTANA has not been evaluated in patients with hepatic impairment *[see Warnings and Precautions (5.6)]*.

As cabazitaxel is extensively metabolized in the liver, hepatic impairment is likely to increase the cabazitaxel concentrations. Patients with impaired hepatic function (total bilirubin ≥ ULN, or AST and/or ALT ≥ 1.5 x ULN) were excluded from the randomized clinical trial.

10 OVERDOSAGE

There is no known antidote for JEVTANA overdose. Overdose has resulted from improper preparation. Please read the entire section *Dosage and Administration (2)* carefully before mixing or diluting. Complications of overdose include exacerbation of adverse reactions such as bone marrow suppression and gastrointestinal disorders. Overdose has led to fatal outcome. In case of overdose, the patient should be kept in a specialized unit where vital signs, chemistry and particular functions can be closely monitored. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

Manufactured by:
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Revised November 2014

CAB-BPLR-SA-NOV14

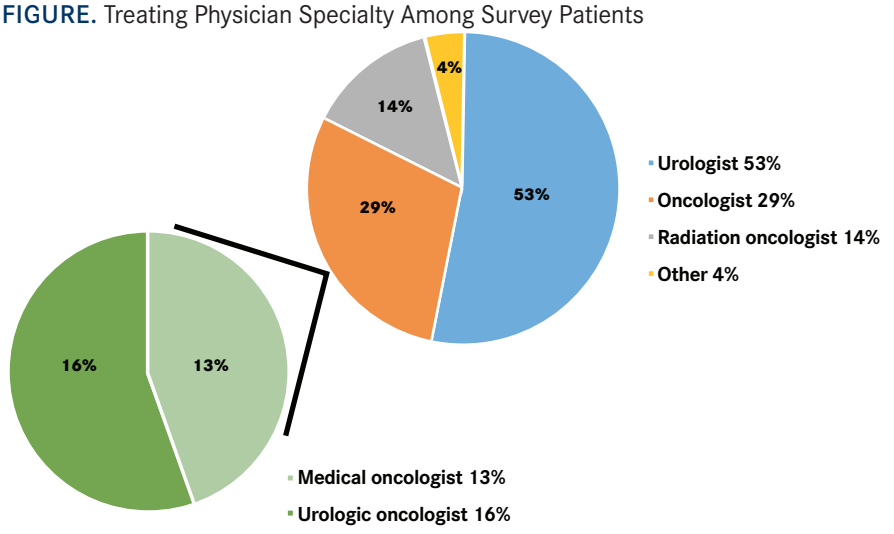
(continued from page SP199)

known to be associated with improved health outcomes and quality of life.

In the absence of a multidisciplinary team, ZERO suggests that newly diagnosed patients, even those diagnosed with a very early stage of the disease, consult with an oncologist so they get a complete understanding of all available treatments, the effectiveness of treatments, and the options available if the cancer returns. In a recent survey by ZERO, only 41% of men with prostate cancer were referred to an oncologist at some point during the prostate cancer journey.

The comprehensive set of educational resources and services, along with cost-sharing assistance, complements the range of integrated services provided by the team of palliative care professionals.

FIGURE. Treating Physician Specialty Among Survey Patients



INSIGHTS INTO THE PROSTATE CANCER JOURNEY

Between November 20, 2013, and January 21, 2014, ZERO conducted a patient education survey to obtain insights into the prostate cancer journey from diagnosis to treatment, survival, and years of active surveillance, which saw participation by more than 1400 patients with prostate cancer, survivors, and caregivers (**TABLE 1**). Among the respondents, 59% indicated they had at some point been diagnosed with prostate cancer, and about one-third of them were undergoing treatment. The survey results provide unique insights into the experiences of prostate cancer patients, their families, and caregivers. In particular, the survey results identify the changing needs of patients and survivors at different points during and after their illness.

TABLE 1. Profile of Caregiver Respondents

RESPONDENT IS CAREGIVER TO	PERCENTAGE
Father	36
Husband	27
Friend	18
Other	19

Additionally, the survey helped describe the needs of the caregivers (24% of survey respondents), which may or may not overlap with the needs of patients and survivors. Initially, more caregivers indicated they cared for a father; however, as disease severity increased, so did the percent of people caring for a husband/spouse/partner with stage IV prostate cancer. Seventeen percent of survey respondents identified that they were associated with the prostate cancer community but did not answer questions on prostate cancer experience.

Education Needs

ZERO's survey results showed that men seek information on prostate cancer at the time of and after diagnosis.

- At the time of diagnosis, patients reported they had a need for information about prostate cancer, treatment options, and side effects. In fact, the survey found that 54% of patients made treatment decisions to avoid certain side effects. While they take care of their loved one, caregivers also strive to understand the disease and its treatment and they pursue resources for emotional support—40% of the caregivers reported experiencing a great deal of stress associated with caregiving.
- At later stages, both patients and caregivers want information on clinical trials, treatment options, and survivorship/life after treatment. Additionally, caregivers are interested in news and information about the prostate cancer community.

According to the survey, men diagnosed with prostate cancer identified ZERO as their preferred source for prostate cancer information, and digital and print materials, videos, blogs, and webinars were chosen as ideal outlets to deliver prostate cancer health education.

Treatment Decision

The survey found that doctors are a trusted resource for information about the specifics of prostate cancer, the treatment options, and the side effects of treatment. Nearly 80% of men who had been diagnosed with prostate cancer said they received information from their healthcare team, and most found it useful. However, the treatment decision is not made in a vacuum: more than half the patients in the survey reported that in addition to their treatment team, a spouse, children, a family member, or a friend had helped them make the decision.

When asked to identify the factors that helped them make their treatment decision, 3 were cited by more than half of the respondents:

- 63% said they chose the treatment based on information from personal research.
- 54% said they chose the treatment because their doctor said it was the best choice.
- 52% said they chose the treatment that provided the best chance of survival.

Multidisciplinary Approach

A medical oncologist was reported as the physician primarily responsible for managing their treatment by 29% of patients in the survey. For the remaining 71%, the physician was either a urologist (53%), a radiation oncologist (14%), or a specialist other than an oncologist (4%) (**FIGURE**).

Of the 71% of patients who did not see a medical oncologist, only 41% said that they had been referred to an oncologist at some point during their prostate cancer treatment. Taken together, the survey results suggest that 58% of the patients had seen an oncologist, including the 29% who were primarily managed by a urologic or medical oncologist and the 29% (ie, 41% of the 71%) who were referred to an oncologist at a later point.

The results suggest a significant opportunity exists to encourage men who are newly diagnosed with prostate cancer to consider involving a medical oncologist in the treatment decision making process and to consider the value that a multidisciplinary team can provide to both the patient and his caregiver (**TABLE 2**).

TABLE 2. Specialists Most Seen in Addition to Physicians

Nutritionist
Social worker
Complementary medicine specialist
Financial specialist

COMPREHENSIVE SUPPORT FOR ADVANCED PATIENTS WITH PROSTATE CANCER

The PAN Foundation and ZERO share the common goal of providing hope and help to men and their loved ones. We recognize that access to the most appropriate therapy can be hampered by a lack of information, and by financial obstacles such as unaffordable copayment amounts. Men with advanced prostate cancer can benefit from the robust patient support services offered by ZERO and the elimination of cost-sharing barriers by PAN. **EBO**

Its critical to round out your team of healthcare professionals with an oncologist to get a full understanding of all available prostate cancer treatments, to give yourself the best chance to beat the disease.

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YOU&i™ Support Program

ELEVATING PATIENT SUPPORT

YOU&i™ Instant Savings Program $10 PER MONTH*

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Monday - Friday, 8 AM - 8 PM ET
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YOUR CONNECTION TO A WORLD OF SUPPORT

YOU&i™ Support Program helps patients understand the insurance process, find cost support options, and gather information along their treatment journey.

*For a 30 day supply of IMBRUVICA® for eligible commercial patients. Not valid for federal and state healthcare program beneficiaries.

imbruvica®
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YOU&i™ Support

www.youandisupport.com

Help patients discover a world of support through the YOU&i™ Support Program, a personalized program that includes information on access and affordability, nurse call support, and resources for patients being treated with IMBRUVICA®.

Help Patients Enroll

To register eligible patients being treated with IMBRUVICA® to begin receiving personalized support:

- Visit **www.youandisupport.com** and click the “Enroll Here” button
- Call 1-877-877-3536, Monday through Friday, 8 am - 8 pm ET; or
- Download the YOU&i™ Support Program enrollment form

Access Support

Once enrolled, patients being treated with IMBRUVICA® will be provided with:

- Rapid (2 business days) benefit investigation
- Information about the prior authorization process
- Information about the insurance appeals process

To help connect patients to a specialty pharmacy, download a current list of specialty pharmacies that are authorized to dispense IMBRUVICA® and are able to service most private and Medicare Part D plans.


imbruvica® (ibrutinib) 140mg capsules

Specialty Pharmacy Provider Network

The following specialty pharmacies are authorized to dispense IMBRUVICA® and are able to service most private and Medicare Part D plans. Prescriptions may be faxed to one of the following pharmacies.

Avella Specialty Pharmacy
Phone: 1-877-546-5779
Fax: 1-877-546-5780
Website: www.avella.com

Biologics
Phone: 1-800-850-4306
Fax: 1-800-823-4506
Website: www.biologicsinc.com

Diplomat Specialty Pharmacy
Phone: 1-877-977-9118
Fax: 1-800-550-6272
Website: www.diplomatpharmacy.com

Onco360
Phone: 1-877-662-6633
Fax: 1-877-662-6355
Website: www.onco360.com

Total Life Care (TLC)
Phone: 1-888-355-4191
Fax: 1-888-355-4192
Website: www.tlcrxpharmacy.com

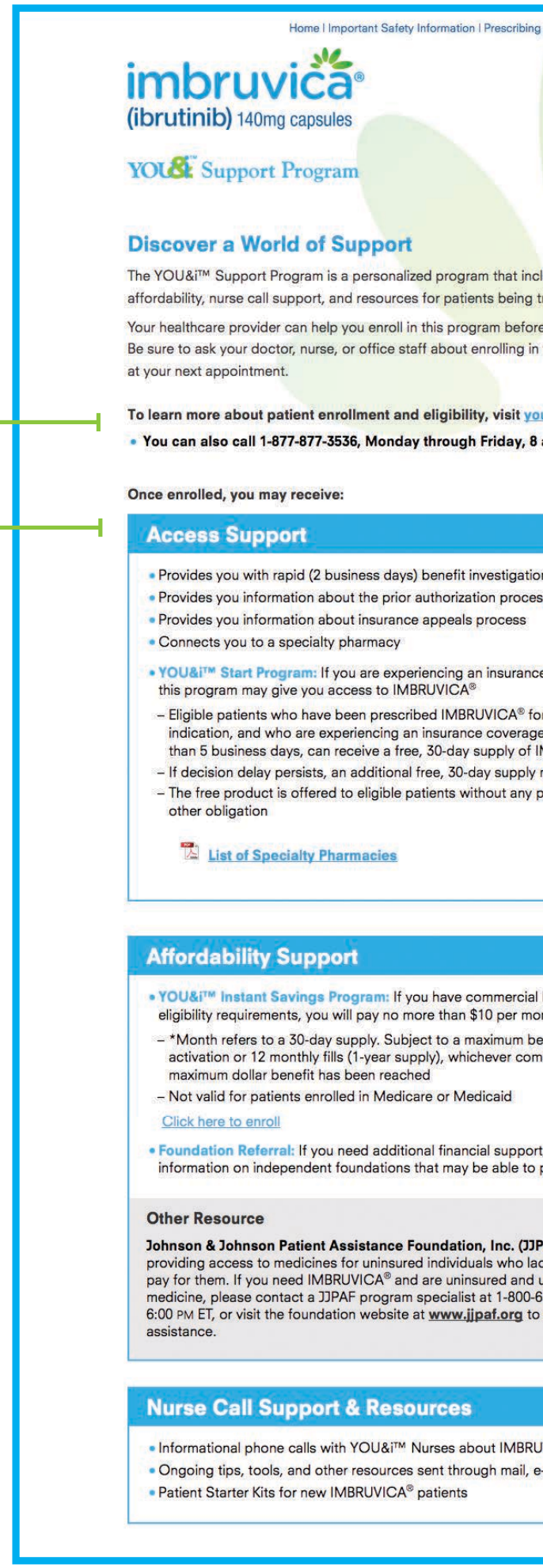
This network of pharmacies will assist providers and patients in obtaining access to IMBRUVICA® through services such as prior authorization assistance and co-pay support for eligible patients. If patients are not eligible for co-pay support, the pharmacy may refer them to the YOU&i Access™ Program, which may be able to provide assistance and support, if needed.

This represents a partial list of pharmacies supplying IMBRUVICA®. It is not intended to serve as a comprehensive list. Pharmacyclics, Inc. and Janssen Biotech, Inc. do not endorse the use of any of the listed pharmacies in particular.

For more information call 1-877-877-3536 or go to www.imbruvica.com

Please see the enclosed Important Product Information for IMBRUVICA®.

YOU&i Access program | pharmacyclics | janssen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YOU&i™ Support Program

Discover a World of Support

The YOU&i™ Support Program is a personalized program that incl affordability, nurse call support, and resources for patients being t

Your healthcare provider can help you enroll in this program before Be sure to ask your doctor, nurse, or office staff about enrolling in at your next appointment.

To learn more about patient enrollment and eligibility, visit yo

- **You can also call 1-877-877-3536, Monday through Friday, 8**

Once enrolled, you may receive:

Access Support

- Provides you with rapid (2 business days) benefit investigatio
- Provides you information about the prior authorization proces
- Provides you information about insurance appeals process
- Connects you to a specialty pharmacy
- **YOU&i™ Start Program:** If you are experiencing an insurance this program may give you access to IMBRUVICA®
  - Eligible patients who have been prescribed IMBRUVICA® fo indication, and who are experiencing an insurance coverage than 5 business days, can receive a free, 30-day supply of IM
  - If decision delay persists, an additional free, 30-day supply
  - The free product is offered to eligible patients without any p other obligation

List of Specialty Pharmacies

Affordability Support

- **YOU&i™ Instant Savings Program:** If you have commercial eligibility requirements, you will pay no more than $10 per mo
  - *Month refers to a 30-day supply. Subject to a maximum be activation or 12 monthly fills (1-year supply), whichever com maximum dollar benefit has been reached
  - Not valid for patients enrolled in Medicare or Medicaid

Click here to enroll

- **Foundation Referral:** If you need additional financial support information on independent foundations that may be able to p

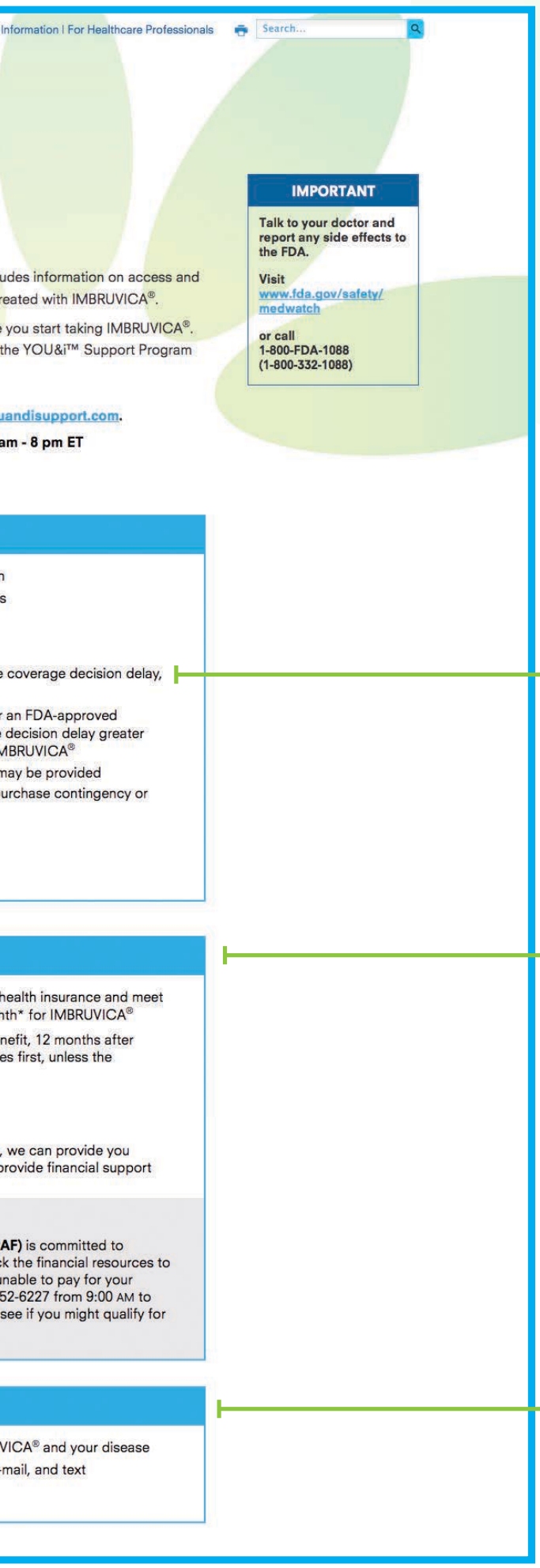
Other Resource

Johnson & Johnson Patient Assistance Foundation, Inc. (JJP providing access to medicines for uninsured individuals who lac pay for them. If you need IMBRUVICA® and are uninsured and u medicine, please contact a JJPAF program specialist at 1-800-6 6:00 PM ET, or visit the foundation website at **www.jjpaf.org** to assistance.

Nurse Call Support & Resources

- Informational phone calls with YOU&i™ Nurses about IMBRU
- Ongoing tips, tools, and other resources sent through mail, e-
- Patient Starter Kits for new IMBRUVICA® patients

Program Mapped!®



YOU&i™ Start Program

Learn about providing eligible new patients with access to IMBRUVICA® during an insurance coverage decision delay.

Affordability Support

Discover the benefits of the YOU&i™ Instant Savings Program, and help enroll patients in the program. Eligible patients will receive instant savings on private insurance co-pays, deductibles, and co-insurance for IMBRUVICA®. Not valid for federal and state healthcare program beneficiaries.

Nurse Call Support & Resources

The YOU&i™ Support Program also offers nurse call support services to provide information and respond to patients' questions about their disease and IMBRUVICA®.

Ongoing tips, tools, and other resources about IMBRUVICA® are sent through mail, e-mail, and text. Patient Starter Kits for new IMBRUVICA® patients are also available.

Please see full Prescribing Information for IMBRUVICA® at **www.imbruvica.com**.

03/15 PRC-00962

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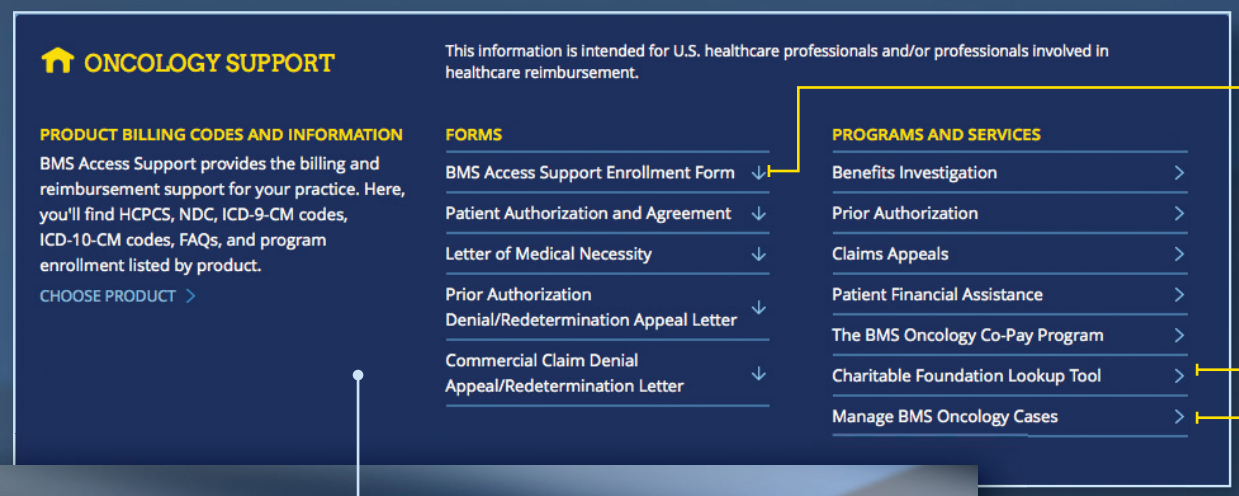
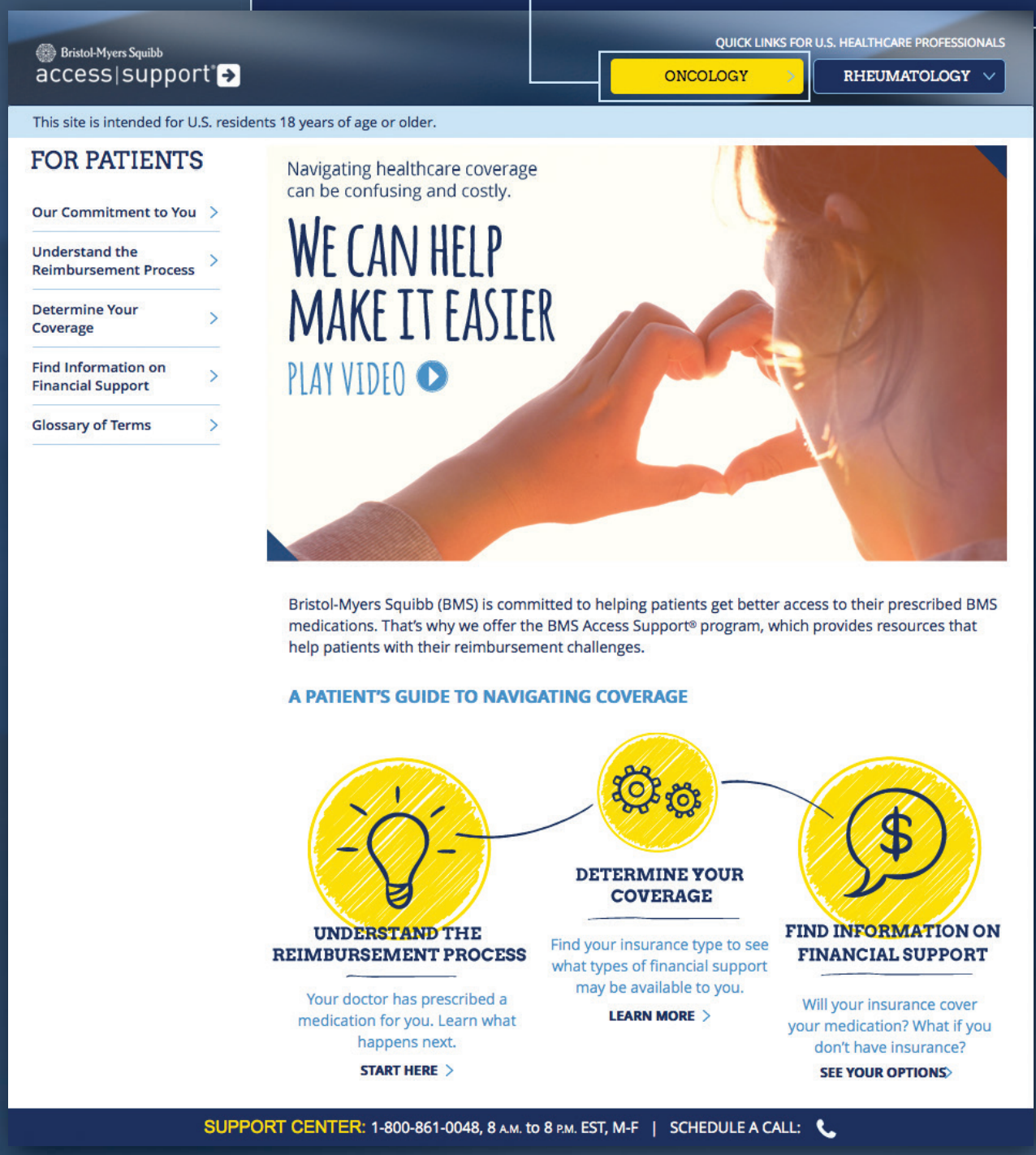
Bristol-Myers Squibb (BMS) is committed to helping patients get access to their prescribed BMS medications. Access Support® provides healthcare providers and their patients with reimbursement information and support services for Bristol-Myers Squibb Oncology products.



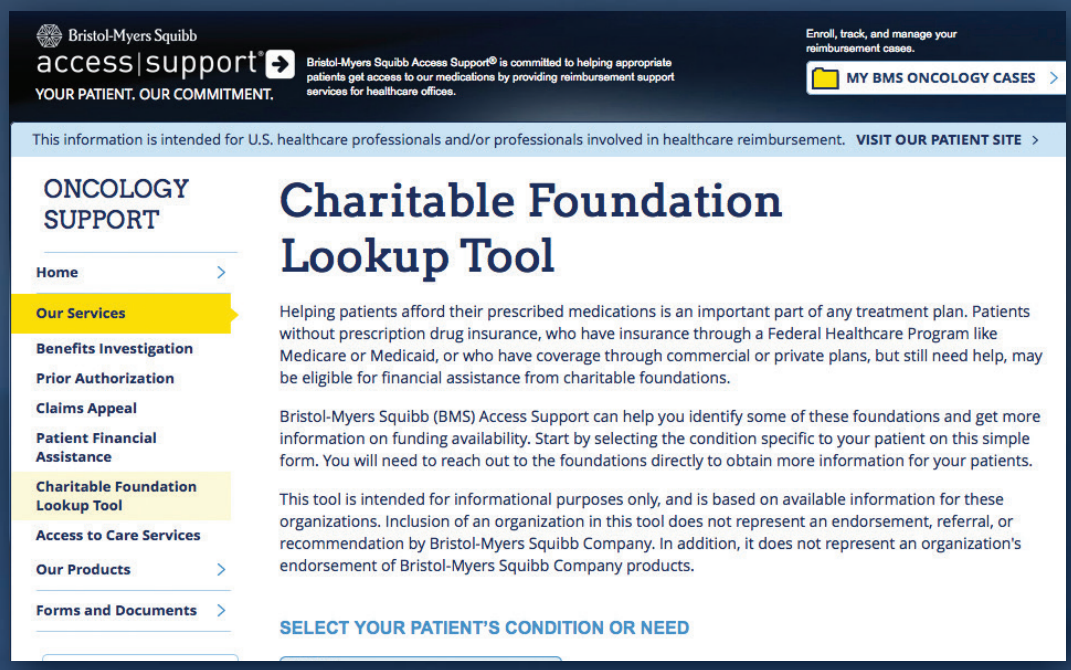


AJMC® Managed Markets Network®

BMS Access Support® Enrollment Form

Single enrollment form for HCP and patients to enroll in the services below for BMS oncology medications. Download, select requested services, complete, and fax this form. If you have any questions, contact us at **1-800-861-0048**.

- **Benefit Investigation**
- **Prior Authorization & Appeals Assistance**
- **Comprehensive Coverage Research**
- **Co-Pay Assistance Referrals**
- **Information About Independent Foundation Assistance Programs**



Charitable Foundation Lookup Tool

For patients who need additional assistance affording their BMS medicines, BMS Access Support® can help identify charitable foundations that may provide more information on funding availability. Utilize the ***Charitable Foundation Lookup Tool*** feature to access information on organizations that may be able to help.

Manage BMS Oncology Cases

The My BMS Oncology Cases program gives your oncology practice the tools to enroll, track, and manage your cases online through an HCP portal.

ONCUS15UB00228-01-01 03/15

Bristol-Myers Squibb

Patient, Physician, and Payer Conversations in Palliative Care
(CONTINUED FROM COVER)

ABOUT THE AUTHOR

BlueCross BlueShield Association

PATTI FOREST, MD, MBA, FAAFP

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suffering serious illness that may be life-limiting. Significant progress in promoting palliative care has been made since the landmark IOM report. Agencies such as the National Hospice and Palliative Care Organization provide free resources to help people make decisions about preferences for treatment at the end of life. The American Board of Medical Specialties formally recognized palliative medicine as a specialty in 2008. In addition, many medical schools and residency programs incorporate palliative care in their training. The American Hospital Association published strategies in 2012 to promote performance improvement in advanced illness management. This work focuses on ways to improve quality of care, increase patient satisfaction, and reduce inefficiencies in the treatment of patients with serious illness.[4] More recently, the Coalition to Transform Advanced Care developed an Advanced Care Model that coordinates care across multiple settings to deliver a patient-centered, high-quality, integrated approach for treatment of individuals with advanced illness.[5] Mainstream media has also entered the dialogue with numerous articles and editorials being published related to the quality of life and financial benefits of palliative care. For instance, a recent article in *The Wall Street Journal* cited examples of patients who were not considered at end of life who greatly benefitted from the physical and emotional support provided by palliative care programs. "Most people who need palliative care are in fact not dying, but have one or more chronic diseases which they may live with for many years,"[6] said Diane Meier, MD, the director of the Center to Advance Palliative Care, in the article, which followed an earlier interview of Dr Meier.[7]

Despite increased awareness and multiple approaches to improving access to palliative care services, there remains significant opportunity for further coordination across the healthcare continuum. Factors contributing to suboptimal use of palliative care services include limited access to services, misaligned payment models, and fragmented care delivery systems. In addition to these obvious barriers, another factor is anxiety on the part of patients, physicians, and payers. Patients may avoid voicing their wishes for fear that they will be denied curative treatment to improve their clinical condition. While many physicians are comfortable discussing end of life preferences, others may hesitate to initiate a discussion due to fear that patients will perceive they have abandoned hope. Payers may avoid developing programs that promote palliative care services for fear of being accused of bias toward reducing medical expenditure for ongoing treatment. These fears are not unwarranted—"death panel" allegations that arose during the early days of the Affordable Care Act amplified the hesitancy to discuss end of life care among patients, providers, and payers.

In light of the controversy surrounding physician payment for end of life discussions, and in an attempt to address barriers to appropriate end of life care, IOM undertook a study to review the current state of care for persons with advanced illness who may be approaching death. The subsequent report, *Dying in America,* was published in late 2014 and outlined recommendations intended to encourage conversation between patients, families, providers, payers, and policy makers with the goal of high quality end of life care that is consistent with an individual's preferences and values.[8] These recommendations include payment reform and policy support, development of evidence-based quality standards, professional education and development, and public education and engagement.

Payment reform is necessary to make palliative care and advanced illness management more accessible and sustainable, and numerous pilot models and initiatives have been launched to achieve the said objective:

- The CMS Innovation Center is testing payment and service delivery models that improve quality and reduce cost of care. The Medicare Choices Model allows Medicare beneficiaries to receive palliative care services (delivered by select hospice providers) while receiving ongoing active treatment for their medical condition.[9]
- This year, the American Medical Association released procedure codes for payment of advance care planning services. The availability of these codes paves the way for providers to get reimbursed for discussions with patients and families around end of life and advanced illness management preferences.[10]
- In 2014, the Center to Advance Palliative Care published a tool kit that identifies opportunities to integrate palliative care services in payer-provider partnerships and offers examples of initiatives already implemented by leading payer organizations.[11]

Despite increased awareness and multiple approaches to improving access to palliative care services, there remains significant opportunity for further coordination accross the healthcare continuum.

PALLIATIVE CARE INITIATIVES ADOPTED BY BLUE CROSS BLUE SHIELD

Blue Cross Blue Shield of North Carolina developed the Blue Quality Physician Program (BQPP) to recognize and financially reward practices that demonstrate a commitment to patient-centered care and focus on improving health outcomes and reducing cost of care. Although developed in 2009 for primary care practices, it is now offered to community-based oncology providers. Participating primary care and oncology practices must demonstrate completion of education modules in cultural competency, palliative care, and advanced illness management. In addition, oncology practices are required to provide documentation to verify that patients receive measurement of functional status at various points during treatment, development, and communication of a cancer treatment plan, along with documentation of goals of care. The number of palliative care and hospice referrals from the oncology practice is also tracked. BQPP has gathered encouraging results from this pay-for-performance program. While primary care practices in the BQPP program demonstrate improved quality over peer practices, early results from the BQPP oncology program indicate a high level of commitment to care planning and communication and offering of palliative care services. The cost of care in these practices is generally lower than health system-owned peer practices, with fewer emergency department visits and hospital admissions. Importantly, both provider and patient satisfaction are high.

Value-based reimbursement aligns payers and providers to focus on quality of care, cost of care, and enriching the patient experience. Increased transparency improves consumer awareness of costs, and helps them play a critical role in the value of care conversation. With approximately one fourth of Medicare spending occurring during the last year of life,[12] the potential cost savings achieved by comprehensive advanced illness management and palliative care services is significant. For example, Sutter Health's Advanced Illness Management program demonstrated a cost reduction of $5000 per patient at 90 days post enrollment,[13] coupled with very high patient and caregiver satisfaction.

Palliative care should not be reserved for individuals at the end of life, but should also be widely available for patients with conditions involving treatment with temporary but severe side effects. As new models become available to deliver palliative care to a broader population, the stigma for palliative care services can be reduced by focusing on relieving pain and suffering, regardless of the life expectancy of the patient. Advanced illness management may be a more acceptable term that encourages earlier dialogue between patients and physicians. Public engagement to advocate for policies to support palliative care services is an important component in aligning funding priorities. It is also important for consumers to help guide payers in development of advanced illness and palliative care programs as well as benefit designs. Together, these activities will increase transparency and decrease fear of end of life conversations among patients, providers, and payers. As we replace fear with empowerment, we will further improve the quality of care at the end of life. **EBO**

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PROVIDER PERSPECTIVE

Trading Conflict for Synergy

(CONTINUED FROM COVER)

was a team, and what was needed was a way to pay for that team. Palliative care, like cancer care, is best accomplished by a coordinated interdisciplinary team that encourages multiple perspectives from dedicated and inspired professionals who work together to deliver value to patients on their own terms. Because the payment model is fee-for-service, a palliative care doctor can't generate the revenue required to support his or her own salary, let alone support a team of professionals. Despite the value a palliative care team can bring to a patient with a serious illness such as cancer, and their families, as well as to oncologists and their professional teams, I failed to secure funding for a medical assistant, let alone a nurse, social worker, chaplain, or administrative help—just the familiar refrain to "do more with less." As many doctors are aware, when physician billing is the only engine for generating revenue, it is more likely that things will get done *to* patients than *for* them. Also, providers burn out like crazy and treat one another poorly.

IMPROVING VALUE WITH REFINED PAYMENT MODELS

Value-based payment models are imminent, and we must be equipped to make that fresh approach work for all of us—centering care on the patients and ensuring sustainable work for the professionals they count on. Since teamwork by coordinated professionals is technically necessary to deliver comprehensive care to cancer patients, doesn't it make sense to pay on the basis of an agreed-upon goal? Additionally, doesn't it make sense to define that goal with the patient at its center? In our eternal battle with payers, it never occurs to us that if we are all committed to patient-centered care, our interests are entirely aligned. The Triple Aim of improved quality of life, improved patient experience, and reduced costs defines value in terms that get us all to the table. Integrated, team-based palliative and cancer care can't help bringing value to patients and their families by much more effectively managing symptoms, extending life when possible, and replacing desperation-driven expenditures with value-based support.[2] We are swiftly met by improved performance status, less distressed patients and families, and even longer survival.[3] Because integrated palliative and cancer care is less costly, the sustainability of care delivery is as important to payers as it is to you, your patients, and our care teams.

WHO WE ARE

ResolutionCare is here to help by extending the capacity for community palliative care in California and supporting oncology practices as they work hard to improve the basic palliative care skills of their teams. At its heart, ResolutionCare is an independent rural palliative care team. But we are also a tandem social enterprise consisting of:

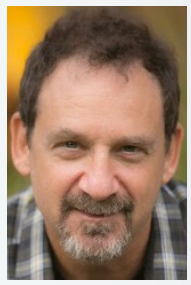
- a community-based, home-centered clinical practice structured as *ResolutionCare PC*, and
- a distinct educational nonprofit entity, *ResolutionCare Fund* (a fiscally sponsored project of Community Initiatives, a 501(c) 3 organization).[4,5]

Both have the same mission: "Bringing capable and compassionate care to everyone everywhere as they approach the completion of life." *ResolutionCare PC* offers people with serious illness access to specialty palliative care clinical services in their homes through the innovative use of videoconferencing, a nimble interdisciplinary team, and value-based payment models. *ResolutionCare Fund* uses the same videoconferencing technology and interdisciplinary team through a rigorously defined Resource Sharing Agreement. As a licensed affiliate/partner with the University of New Mexico's Project ECHO model,[6,7] we will use this powerful learning model to enhance the basic palliative care skill set of a diversity of healthcare providers in a diversity of practice settings where people with serious illness receive care, like medical oncology practices and cancer care programs.

By using videoconferencing, our clinical programs have "rediscovered" the power and impact of house calls. Some cancer patients will make more than 150 trips in the last year of life for infusions, physician appointments, lab draws, imaging, and fractionated radiotherapy. Faced with these numbers, it is not surprising that patients love house calls when they have the opportunity, and they view a videoconference with their provider as a very similar experience.[8] From a professional's perspective, it's the rule rather than the exception that vexing problems are clarified and that practical and relevant information is reliably and almost instantly gained in this way. For example, upon walking in the door, you might see how badly confused your patient is with the jumble of medications accumulated over years of fragmented care, or perhaps discover the drug-diverting dependent son whom you hadn't known existed. Whether the house call is virtual or face-to-face, whether it is performed by trained community health workers, nurses, social workers, chaplains, or physicians, this approach eliminates the expense associated with the infrastructure of an outpatient clinic and puts the resources thus freed up to work for people with cancer in more efficient ways. By the way, home-based, community-centered palliative care saves money…tons of the stuff! That's why CMS,[9] the California Healthcare Foundation,[10] Cambia Health Foundation,[11] Partnership Health Plan of California,[12] and many other insurers are investing heavily in community-based specialty palliative care, value-driven payment models, and collaborations that put more and better basic palliative care skills (symptom control, advanced care planning, shared decision making, etc) to work for cancer patients.

Our educational programs are built on the solid foundation of Project ECHO, a powerful and disruptive innovation in knowledge sharing that "demonopolizes" expertise. Project ECHO is a case-based learning approach that leverages videoconferencing technology, linking the scarce resource of a specialty team (eg, palliative care team) with up to 10 teams (eg, oncology practices) in a hub-and-spoke fashion. Applied to a busy community oncology practice, the oncology team at the spoke might consist of clinic and infusion nurses, mid-level practitioners, practice managers, and oncologists, as available. A typical schedule involves up to 6 case presentations, deidentified and prepared by the various linked oncology teams. Meet-

ABOUT THE AUTHOR



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ing twice monthly for 90 minutes (including a didactic component for CEU/CME), the value accumulates quickly as knowledge and insight move bidirectionally from oncology to palliative care and vice versa, not to mention from oncology spoke to oncology spoke. Through rigorous data collection and analysis, ResolutionCare hopes to demonstrate that oncology practices will track the improved quality of life, satisfaction, and perhaps even duration of survival of the patients in participating oncology practices. In addition, ResolutionCare's programs are designed to study how our interventions are at least cost neutral. Most likely, the payers will enjoy substantial cost savings and an excellent return on investment. We are also committed to making certain that all cancer professionals—medical oncologists, surgical oncologists, radiation oncologists, oncology nurses, nurse practitioners, and primary care providers—feel better and enjoy the satisfaction that comes from being a part of an integrated team.

Should we defend the status quo in the face of the demographic tsunami of aging Baby Boomers, the unsustainable stratospheric costs of cancer care, and the challenges and dissatisfaction of our cancer patients and colleagues when we simply want the best for all involved? I think it's best if doctors and allied cancer professionals work together synergistically and invest in the future with innovation, taking care of our teams and of us. If ResolutionCare can be of assistance, we are honored to lend a hand. If you are interested in helping ResolutionCare to find the funding for this bold innovation, please lend us yours. **EBO**

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COST OF CARE

The Role of Palliative Care in Accountable Care Organizations
(CONTINUED FROM COVER)

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Sharp Healthcare notes that the average enrollment for patients on their Transitions program is 5 months, and 75% of enrollees ultimately transitioned to hospice with an average hospice length of stay exceeding the national average.

healthcare costs.[4] This population is characterized by both chronic conditions and functional limitations. Notably, most (89%) high-cost patients are not in the last year of life.[5] Despite the intensity of spending, quality of care for this group is often low, marked by poor communication, high burden of pain and other symptoms, low satisfaction, and preference-discordant treatments.[6-9]

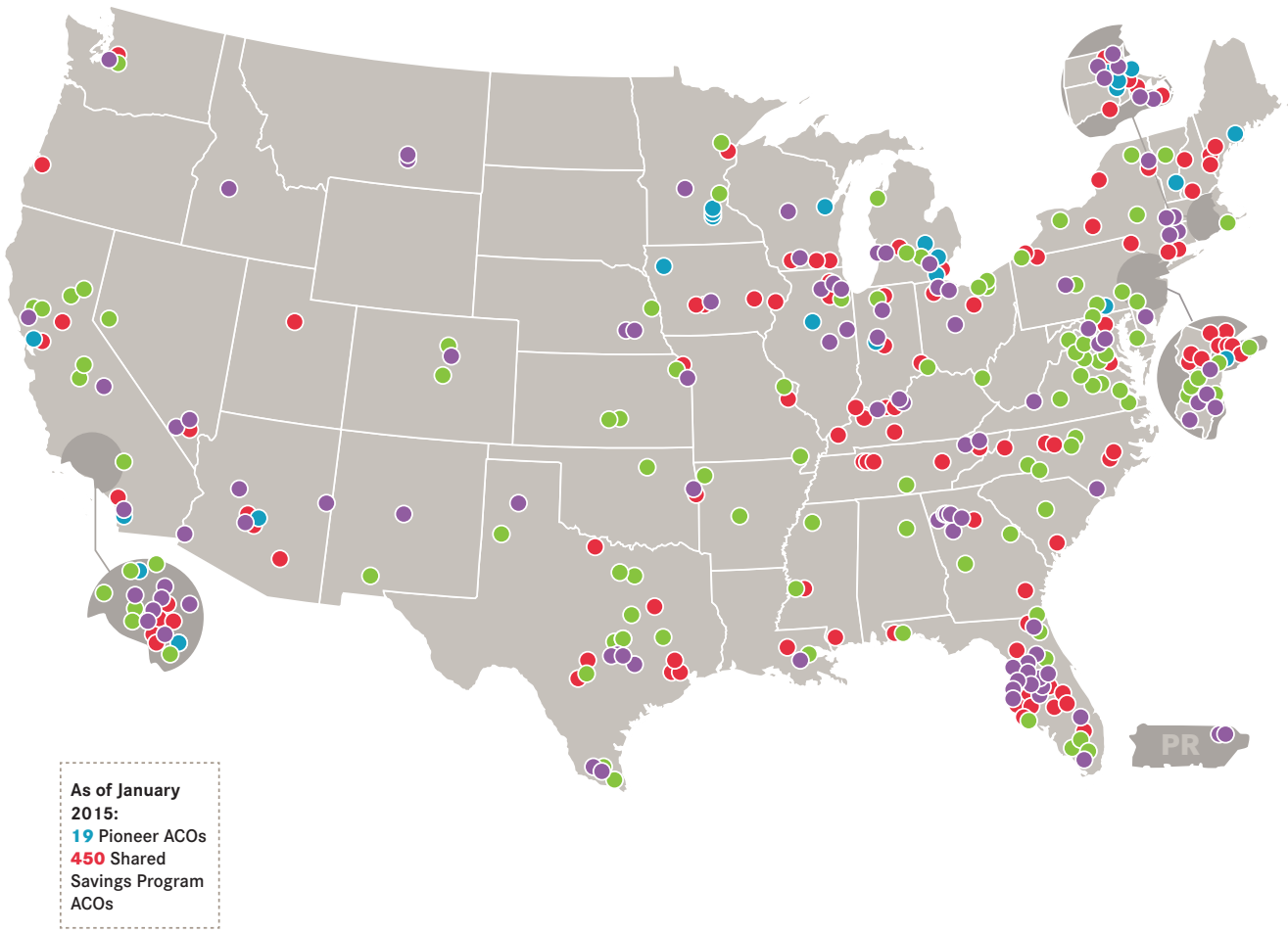
Data consistently demonstrate that palliative care improves quality of care for the seriously ill, and in so doing reduces need for emergency services and hospitalization. Compared with usual care, palliative care for seriously ill patients has been shown to reduce symptom distress,[10-12] enhance quality of life,[11-13] and decrease spiritual distress.[14,15] Additionally, all studies that have compared patients receiving palliative care with those receiving usual care have shown equivalent survival rates and, in fact, palliative care interventions among select groups showed improved survival.[11,16]

Direct and indirect evidence suggests that palliative care also enhances family outcomes. Studies of palliative care and hospice have demonstrated improved family satisfaction and quality of life, decreased depression and anxiety, better bereavement adjustment, and improved survival among spouses.[8,17-20] Indirect evidence supports possible mechanisms for these benefits. For example, families of patients receiving palliative care consultation reported greater attention to their emotional and spiritual needs and enhanced self-efficacy, compared with routine care.[21] Those who could recall a discussion of goals of care—a key component of palliative care—experienced improved patient and caregiver quality of life, lower risk of major depression, and fewer feelings of regret.[18,19] Furthermore, palliative care, and the discussion of goals of care in particular, is associated with lower rates of death in an intensive care unit and decreased use of other forms of high-intensity medical intervention,[22] which have been linked to post-traumatic stress disorder and prolonged grief disorder among bereaved family members.[18,19]

Research has also demonstrated that the improved quality of care associated with palliative care leads to lower costs through prevention of symptom crises, by reducing depression, supporting family caregivers, and matching treatments with patient priorities (such as receiving care at home). To date, 15 studies have examined the effect of inpatient palliative care on hospital costs and all have found an association with reduced costs.[23] A smaller group of studies has also demonstrated that outpatient palliative care can reduce costs and utilization across the entire course of illness.[23,24] For example, a randomized controlled trial (RCT) of outpatient palliative care, in addition to standard oncologic care, among patients newly diagnosed with stage 4 non-small cell lung cancer found that those in the palliative care intervention group had better quality of life, improved survival (a gain of almost 3 months), lower rates of emergency department (ED) visits and hospital admissions within the last 30 days of life, were less likely to receive chemotherapy within the last 14 days of life, and were more likely to be referred to hospice 4 days or longer prior to death—measures indicative of higher quality and lower costs.[11] Similarly, an RCT of a home-based palliative care program demonstrated improved satisfaction, fewer hospital and ED visits, and lower costs.[25] Finally, an RCT of palliative care consultation in a primary care clinic setting resulted in fewer primary care and urgent care visits, yet no difference in use of the ED and hospital.[26]

While quality, the numerator of the value equation, is clearly of greatest priority, the importance of palliative care's impact on costs cannot be ignored. In particular, ACO leadership—charged with providing high-quality care for a population of patients within strict budgetary constraints—have taken notice

FIGURE. Geographic Distribution of Accountable Care Organizations (ACOs) in the United States



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and many are embracing palliative care as a high-value solution for their highest risk patients. To date, over 70% of all ACO hospitals and 82% of ACO hospitals with 50 or more beds have active palliative care programs.[27]

CHARACTERISTICS OF SUCCESSFUL ACO PALLIATIVE CARE PROGRAMS

Successful ACO palliative care programs share several key characteristics. First, these programs attempt to identify and target the high-need and high-risk patient population, preferably before a crisis hospitalization. The specific methods and criteria for patient selection vary, but most include quantitative risk-prediction models, prior utilization of acute care services (eg, ED or hospital admission) and qualitative assessments from the medical record, interviews with patients or families, or referral by clinicians. Quantitative risk-prediction models, which typically include age, gender, medical diagnoses and procedures, prescription use, and/or prior utilization or health expenditure, may be easy to implement but may fail to identify key predictors of risk for future utilization, including patients with functional impairment, cognitive impairment, frailty, social determinants of poor health (such as lack of food and housing), and caregiver burden.[28]

Second, successful programs use trained staff and/or facilitators to elicit individualized patient goals that are then used to guide care plans. This goal-setting, comprehensive needs assessment (including medical, behavioral, and social issues), and care plan development process contributes toward building a personal relationship between the patient, the family, and the care team or care coordinator. The care plan integrates medical services, including expert pain and symptom management, with social and psychological/behavioral health support to meet the individual patient and family needs. The goal is to help patients remain as independent as possible, staying home and avoiding the ED and the hospital.[29]

TABLE 1. Success of the Transitions Advanced Illness Management Program[30]

Average patient enrollment	5 months
Enrollees transitioning to hospice	75%
Hospice length of stay	120 days*
Reduction in ED visits	57%
Reduction in hospital readmissions	54%
Reduction in cost of care	43%

ED indicates emergency department.
National average is 72 days.

Another key characteristic of successful palliative care programs is attention to the patient's family and social support. This involves an assessment of family capacity and willingness to provide care, evaluation of social and financial resources, as well as access to telephone support for patients and their caregivers, 24 hours a day, 7 days a week (www.capc.org/payertoolkit).

Finally, these programs offer flexible "dosing" of services, with the intensity of the intervention and services provided scaled to patients' needs, which fluctuate over time and over the course of a complex, serious illness. This flexibility allows programs to maximize the efficiency of their own resource utilization.

A CASE STUDY OF ACO PALLIATIVE CARE INTEGRATION: SHARP, CALIFORNIA

Sharp HealthCare in San Diego, California, has developed the Transitions Advanced Illness Management program in conjunction with their affiliated Pioneer ACO.[30-32] Additional payer relationships with this program include Medicare Advantage and other private managed care contracts, but not Medicare fee-for-service. The cornerstone of the program, which aims to provide individualized, home-based palliative care for patients with serious illness—including those with progressive functional and nutritional decline—is a goals of care discussion with a skilled facilitator, followed by the development of a personalized care plan. Key features of the Transitions services include in-home patient and family education, medication reconciliation, counseling on what to expect and what to do if a crisis arises, caregiver assessment and support, completion of advance care planning and documentation (eg, Physician Orders for Life Sustaining Treatment forms), and expert symptom management.

Sharp notes that the average enrollment for patients on the Transitions program is 5 months, and 75% of enrollees have ultimately transitioned to hospice with an average hospice length of stay far exceeding the national average: 120 days, compared with 72 days. In addition, the program has significantly reduced acute care utilization, including a 57% reduction in ED visits, 54% reduction in hospital admissions, and 43% reduction in total costs of care.[30]

CONCLUSION

To strengthen value, ACOs are working to improve the quality of care and in so doing reduce reliance on avoidable emergency and acute care services for the highest risk, highest cost patient population. Palliative care, an essential partner in this work, has consistently demonstrated its ability to maximize healthcare value, specifically for seriously ill patients with the greatest need and highest risk. Successful programs that have integrated palliative care within an ACO share the following key practices:

- They rigorously target the high-risk population and proactively offer palliative care services.
- They engage in highly skilled discussions of patient goals and personalize care plans to match.
- They assess family and social resources and explicitly address these needs.
- They provide expert symptom management and coordinated medical care across settings.

- They offer maximum flexibility with round-the-clock phone support and service intensity scaled to meet patients' needs as they change over time.

Providers seeking to develop a palliative care program within an ACO or other innovative payment model may find additional resources and support at www.capc.org/payertoolkit. **EBO**

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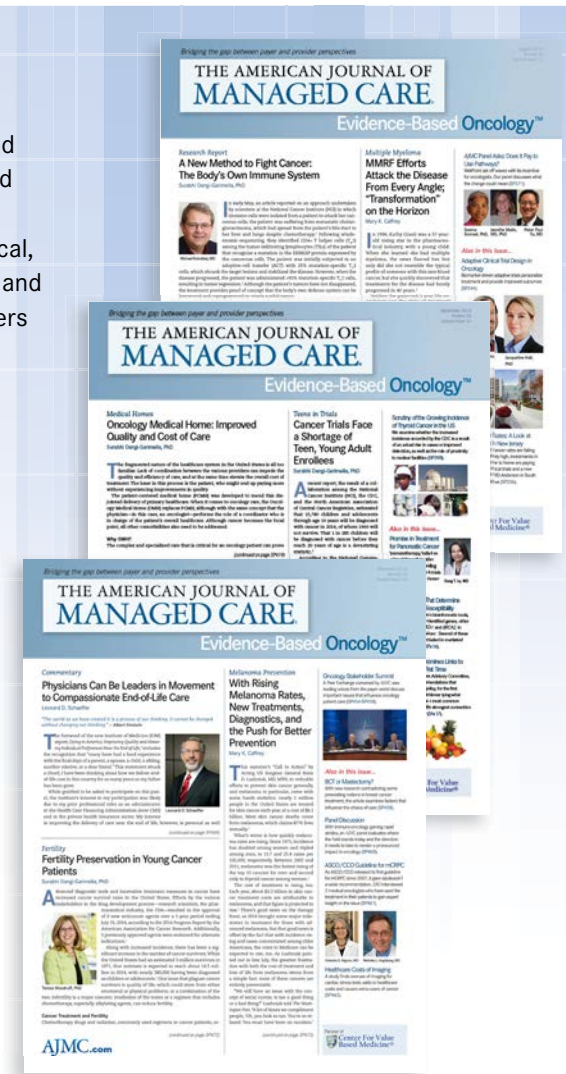

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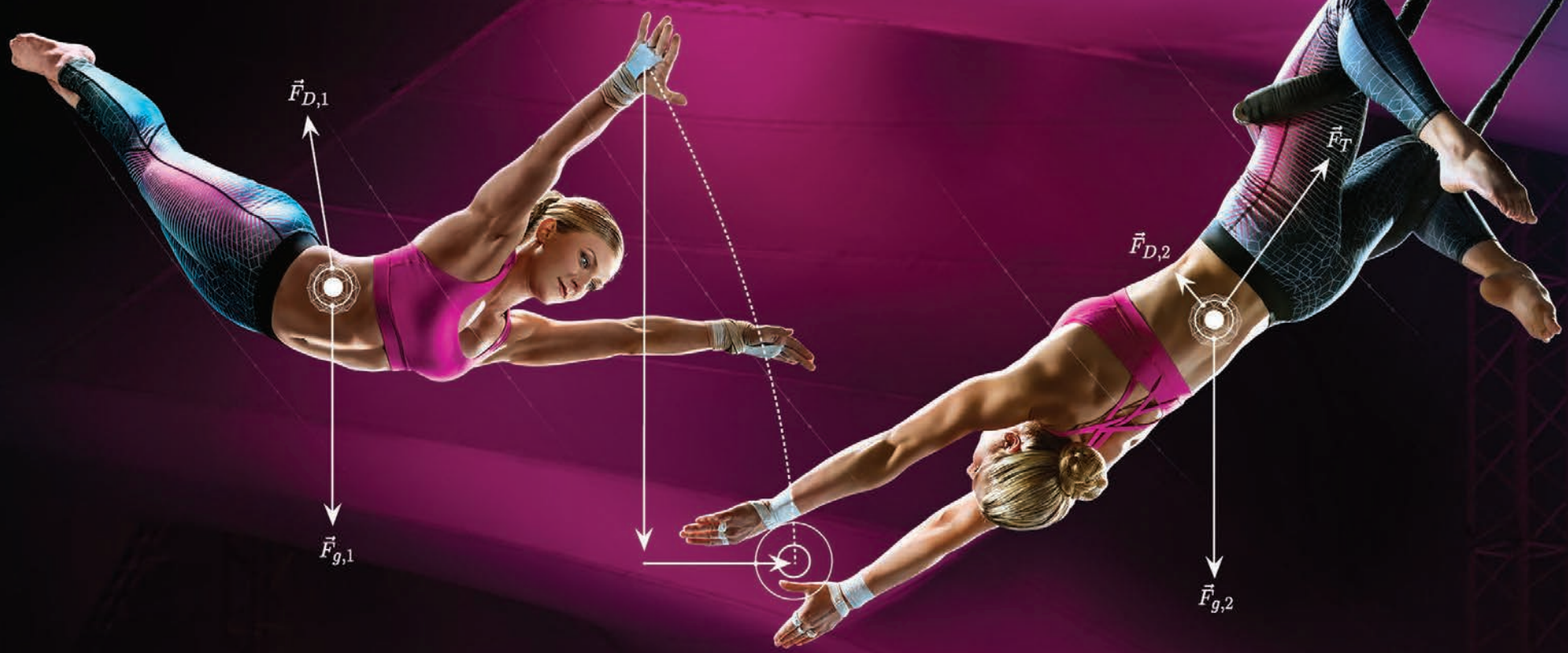

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