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THE CARDIO-ONCOLOGY SPECIAL ISSUE

Provider Perspective

Cardio-Oncology: *The Intersection Between Cancer and Cardiovascular Disease*

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Cardio-oncology, or onco-cardiology, is the discipline that focuses on the intersection of cardiovascular disease and cancer. With the prognosis for many cancers improving, we are seeing an appropriate sharpening of focus on the cardiovascular risks of patients who have survived cancer or are being treated for cancer, as well as a growing recognition of the impact this competing morbidity has on both short- and long-term health outcomes.

Seminal studies demonstrated the increased risk of left ventricular (LV) dysfunction or cardiomyopathy in survivors of childhood cancer who had been treated with anthracyclines and chest radiation.[1,2] Similarly, there are increased risks of congestive heart failure in adults treated with anthracycline-based chemotherapy regimens, which in current practice includes patients with breast cancer, leukemia, lymphoma, sarcoma, and other cancer types.

Along with the traditional approaches of chemotherapy, a revolution in the understanding of the molecular mechanisms that underlie many common cancers has led to the development of targeted pathway inhibitors, many of which inhibit tyrosine kinases. The number of these targeted therapies has increased exponentially in the last decade, with many more in clinical trials. Ideally, these drugs would target only cancer cells, but the potential for cardiovascular effects exists due to the presence of identical molecular pathways in cardiovascular cells.[3]

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Patient Perspective

Radiation Therapy and Cardiotoxicity: *A Cancer Survivor's Story*

DEBRA MADDEN

It all began as a typical afternoon when I was in my office, working as a medical transcriptionist at a local neurology practice. I was organizing a few patient charts that had just been brought in by the last few neurologists as they headed out for the day. What I was doing was not physically taxing in any way, and I was not feeling particularly stressed. But in that moment, I became unaccountably aware of my heart—that it suddenly seemed to be racing uncontrollably, pounding and galloping in my chest. I immediately sat down, breathed deeply, and waited for the sensation to stop. Fortunately, it quickly did, and I pushed the experience out of my mind.

But only a day or so later, as I was walking on my treadmill at home, I realized that strangely enough, my left arm was repeatedly, and of its own volition, rising toward the ceiling. Just as I was wondering "What on earth am I doing?" I felt a heavy, crushing sensation in my chest. I quickly stepped off the treadmill, and the feeling went away almost immediately. Even then, I was not ready to acknowledge that something was terribly wrong. Yet later that same night, there was simply no denying it: as I was resting in bed, the crushing sensation returned, and I began to feel inexplicably, frighteningly short of breath—and so it finally clicked that I needed help.

While speaking with my primary care provider (PCP)'s office the next morning, I was told they had an opening in a few weeks. I almost accepted that…but at that very moment, a long-buried memory came roaring back, loudly insisting, "Tell them about

(continued on page **SP293**)

Healthcare Policy

Advancing Patient Care in Cardio-Oncology: *The ACC.15 Cardio-Oncology Intensive*

TOCHI M. OKWUOSA, DO; AND ANA BARAC, MD, PHD

While many advances in cancer therapeutics have significantly impacted the cardiovascular (CV) health of cancer patients and cancer survivors, transforming lives and growing the population of patients living with and surviving the disease, they have also created a need for a comprehensive and revised approach to the CV care of these patients. Professional medical societies have a long-standing legacy of improving patients' health by providing and developing education, training, clinical guidance, and research resources for their members. To better assist its growing membership in these ways, the American College of Cardiology (ACC) formed a Cardio-Oncology Working Group charged with assessing existing practices along with the needs of patients and professionals in this field. The Group conducted a nationwide survey focused on cardio-oncology services, gathering opinions from CV division chiefs and fellowship training directors. This helped identify important challenges, including the need for broader educational opportunities and training.[1]

ACC.15 CARDIO-ONCOLOGY INTENSIVE

Traditionally, cardio-oncology has been represented at national cardiology conferences with cardiotoxicity-related sessions embedded in focused clinical pathways—most commonly, heart failure and CV imaging. These sessions successfully highlighted novel developments within specific areas, but struggled with introducing a

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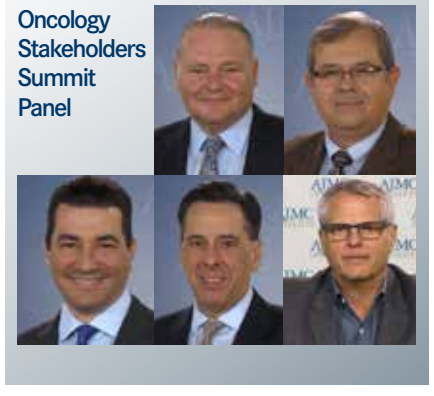
Also in This Issue…



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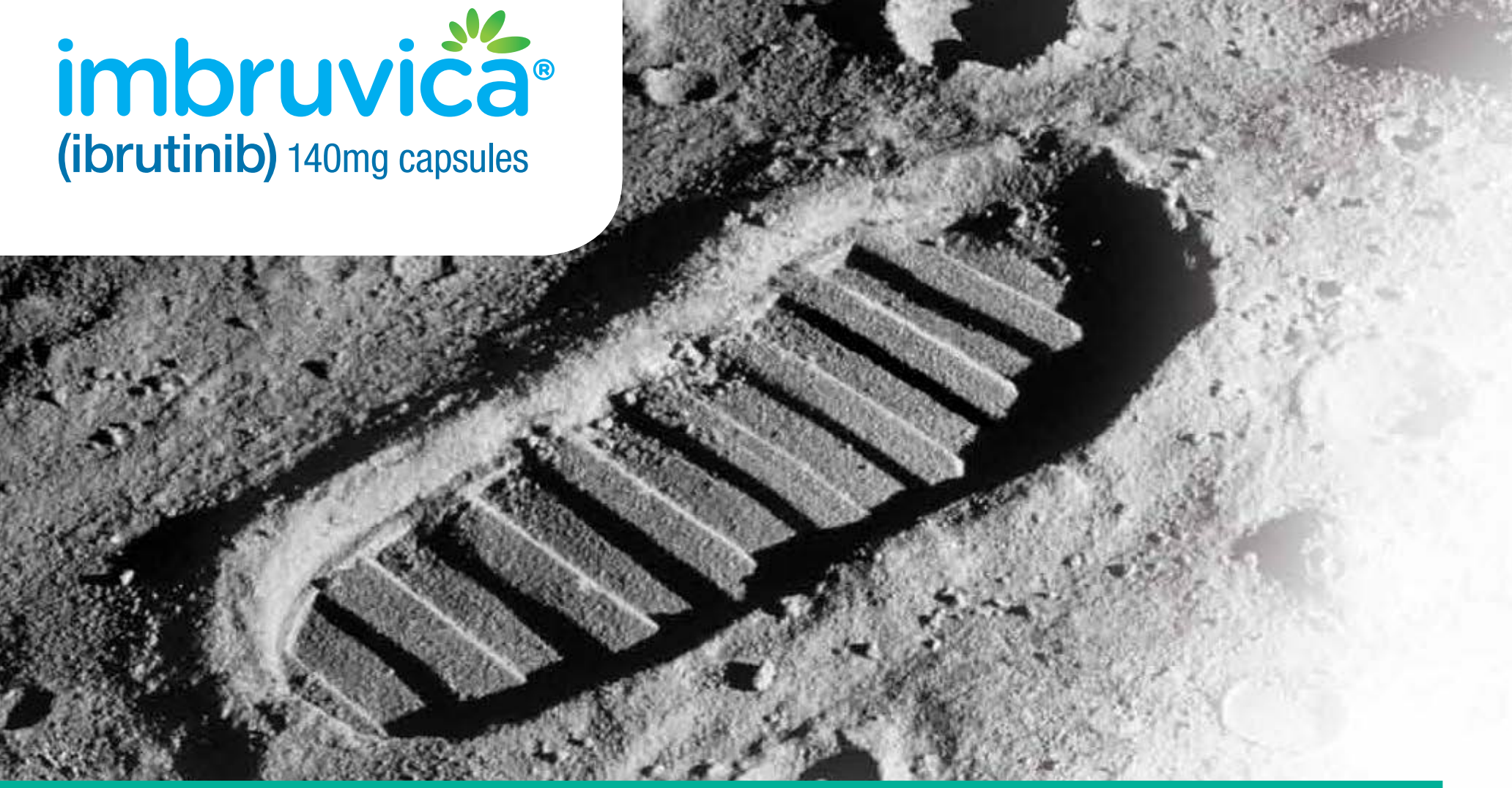

DISCOVERING HOW FAR THERAPY CAN GO

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].*
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration.

Active ingredient made in China.

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

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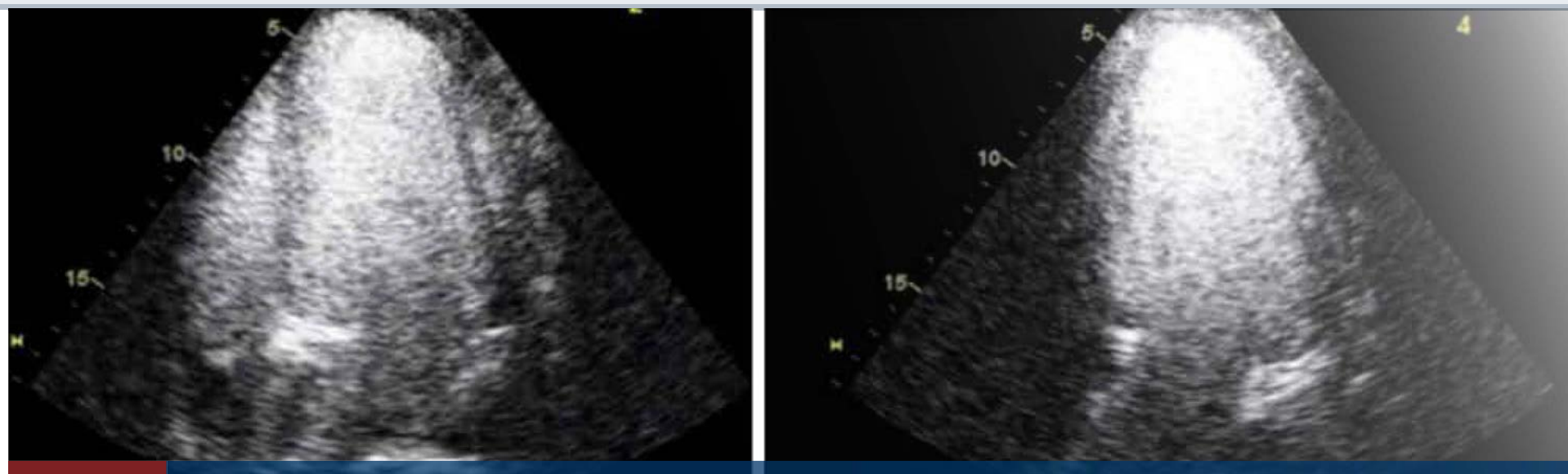
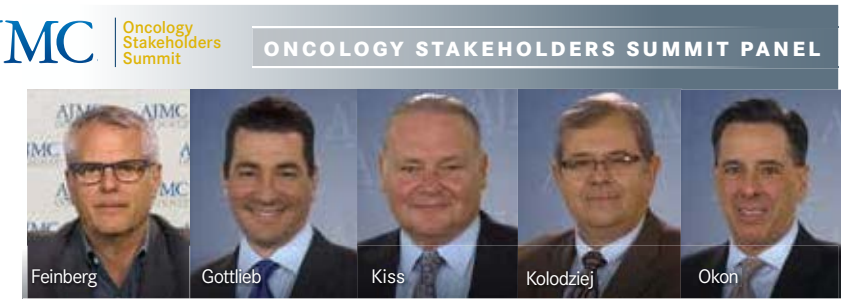


SP295 *Risk-determining stress echocardiogram in a woman with B-cell lymphoma, prior to chemotherapy initiation. Read more about the case study and the American College of Cardiology's Cardio-Oncology Working Group on page SP295.*



Improved Awareness on Cardiotoxicity Among Cancer Survivors


MIKE HENNESSY

Welcome to the June issue of *Evidence-Based Oncology*. With this issue, we hope to draw your attention to an aspect of cancer treatment that took a while to be recognized—cardiotoxicity.

Despite the existence of data highlighting the cardiac effects of some of the older generation of chemotherapy agents, such as anthracycline and docetaxel, lack of awareness among providers has at times resulted in survivors suffering from their harmful effects. But in recent years, several leading cancer centers in the United States have developed dedicated cardio-oncology programs that bring together oncologists and cardiologists to help manage cardiac symptoms associated with cancer treatment. Additionally, agree several of this issue's contributors, implementing preventive measures has been made easier by today's increased emphasis on identifying high-risk or vulnerable patients, including pediatric and geriatric populations, and individuals with preexisting cardiac conditions.

In this issue, we hear from several experts who have either managed or are a part of cardio-oncology programs at Massachusetts General Hospital, MD Anderson Cancer Center, and Brigham and Women's Hospital, and other leading cancer facilities. The issue also includes an article by members of the Cardio-Oncology Working Group formed by the American College of Cardiology (ACC.15), which provides an overview of some of the discussions at this year's Cardio-Oncology Intensive. An article by researchers from Wayne State University School of Medicine delves into what we know about late cardiac effects in childhood cancer survivors and current advances that can help regulate some of the toxicities associated with treatment.

Finally, this issue features a firsthand report from a cancer survivor, who talks about the need for raising awareness about self-care among both patients and providers. Debra Madden's act of personal responsibility changed the course of her treatment for life-altering morbidities associated with cancer treatment.

Please look for our special issue from the annual meeting of the American Society of Clinical Oncology that was recently held in Chicago.

As always, we appreciate your readership. Updates on our live meetings and our conference coverage are available at www.ajmc.com.

Sincerely,

Mike Hennessey
CHAIRMAN AND CEO

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.

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.

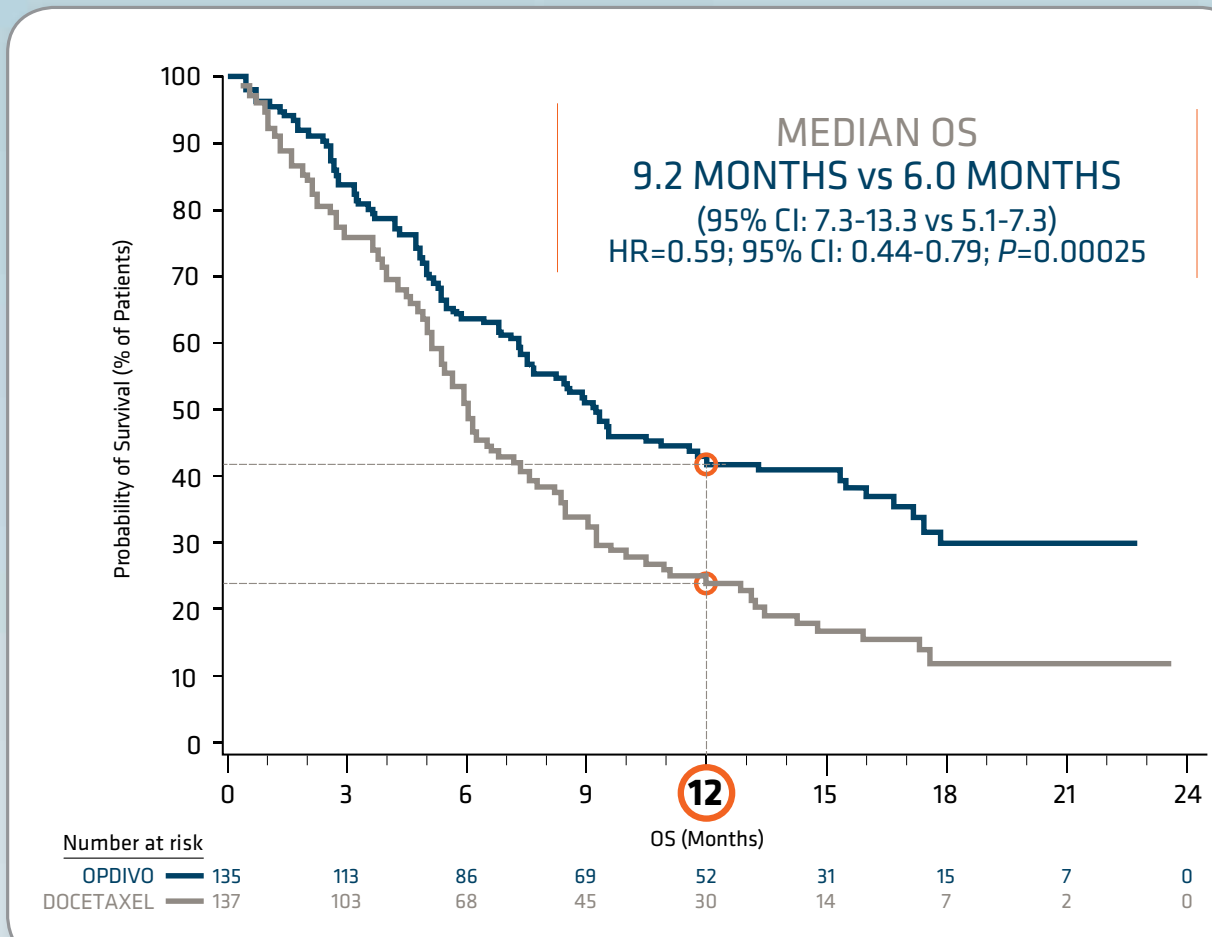
SELECT IMPORTANT SAFETY INFORMATION

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

(Continued)

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 (nivolumab) (n=117)	
	All Grades	Grades 3-4
	Percentage (%) of Patients	
Investigations		
Decreased weight	13	0.9
Infections and Infestations		
Pneumonia[g]	10	5

* 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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Cardio-Oncology: A Sign of How Far We Have Come

Joseph Alvarnas, MD

Siddartha Mukherjee's book, *The Emperor of All Maladies,* and the recent PBS documentary of the same name provide an important historical perspective on the enormous scientific and human struggle that has led to today's profound advances in the war on cancer. In the early days of chemotherapy and radiation therapy, doctors and patients worked together in a desperate battle to defeat a seemingly unstoppable enemy, and progress was marked by near equal parts scientific success and human tragedy. Some of the great early therapeutic successes were fraught with significant treatment-related side effects and unintended long-term toxicities. The radiation therapy that made cures possible for Hodgkin lymphoma led to premature atherosclerotic heart disease. Doxorubicin, an indispensable part of many combination chemotherapeutic regimens, could cause the development of severe cardiomyopathies. Even targeted therapies, such as trastuzumab, could cause significant cardiac toxicity unless used with caution.

During the past 4 decades, survival rates for a number of cancers have dramatically improved; diseases once thought untreatable are now routinely cured. Over time we moved from focusing exclusively on treating cancer to planning for long-term survivorship. The American Association of Cancer Research estimates that 1 of 22 people currently living in the United States is a cancer survivor. Treating and even curing cancer is now simply not enough; ensuring that those who have survived cancer avoid long-term toxicities of therapy is an essential part of effective, best-practice–based cancer care.

Cardio-oncology is the study, management, and prevention of potential cardiac toxicities of cancer treatment. It includes risk mitigation as part of initial treatment planning, monitoring patients for symptoms and complications during the course of therapy, and the development of appropriate cardiac monitoring as part of routine survivorship care. Effective care planning includes the need to recognize that certain cancer patients, including children and the elderly, may be particularly vulnerable to the cardiac effects of treatment. The value proposition of cardio-oncology is that there are enormous human and financial benefits to caring for cancer patients by remaining mindful of the potential cardiac toxicities of treatment and averting these complications through rigorous care planning and pre-planned monitoring.

This edition of *Evidence-Based Oncology* could be considered a primer on cardio-oncology. It includes a retrospective review of research studies that provide an overview of scientific evidence related to the cardiac effects of cancer treatment. In our provider commentaries, we hear about programs that have successfully led to improved awareness and mitigation of cardiac risk for patients undergoing treatment. A commentary by Franco and Lipschultz provides a historical perspective on anthracycline-related cardiac toxicity and the importance of late effects of cancer treatment.

In the early days of cancer care, the primary goal of treatment was survival, at virtually any cost. Based upon a 4-decade leap forward in experience, technology, and increasingly effective therapeutics, our goals are now focused upon the idea of restoring a patient to wholeness. An improved understanding of adverse effects of cancer regimens, such as cardiotoxicity, will help to better prepare us for a move toward a continuum of care model in which we do not view cancer care as being divorceable from the goals of long-term survivorship. These sensibilities will help push us successfully forward through the next 4 decades of cancer care innovation. **EBO**

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Drop-off in Prostate Screening Stirs Controversy

Mary K. Caffrey

To Vanderbilt University's Sam Chang, MD, the drop-off in prostate cancer screening since 2012 represents a "chilling effect." To Otis Brawley, MD, chief medical officer for the American Cancer Society, the change represents more conscientious conversations between doctors and patients.

But whatever one's point of view, the data represented May 18, 2015, at the American Urological Association annual meeting in New Orleans, certainly grabbed headlines: according to a study presented by Ryan Werntz, MD, the controversial 2012 guideline change from the US Preventive Task Force (USPSTF) has triggered a profound shift in clinical practice.[1]

Werntz, a urologic resident at Oregon Health & Science University (OHSU), found that the overall rate of prostate-specific antigen (PSA) testing had dropped 50% among primary care physicians at OHSU since the guideline change.

According to a report from the meeting, published by *OncLive*, the decline was most significant among men aged 50 to 70 years—a group highly likely to benefit from testing.[2]

Werntz and others echoed concerns that were heard immediately in May 2012, when the USPSTF stunned urologists and the cancer prevention community by giving the PSA test a D rating, saying the harms outweighed the benefits.[3] "If you look back before PSA was a big part of prostate cancer screening, 20% to 25% of men would often first see a physician with back pain and be subsequently diagnosed with metastatic disease," Werntz told *Oncology Live*.[2]

USPSTF's 2012 change was rooted in the belief that widespread PSA testing was causing too many men to be biopsied and overtreated for slow-growing cancers that posed no immediate risk. For too many, this caused unnecessary complications such as incontinence and impotence. But supporters of PSA testing say it has saved lives.[4]

In March 2014, Peter R. Carroll, MD, MPH, of the University of California at San Francisco, in presenting updated prostate cancer screening guidelines at the 19th Annual Conference of the National Comprehensive Cancer Network (NCCN) in direct response to the USPSTF, said: "We achieved a 45% reduction in mortality in prostate cancer in the United States, in contrast with an increase worldwide. Yet, the USPSTF gives it a D."[5]

NCCN recommended a middle ground for PSA testing in which screening would be less frequent and be guided by risk factors. Indications for biopsies would be driven by "highly suspicious" digital rectal exams that followed an elevated PSA result.

Brawley, who at the time of the 2012 recommendation was skeptical how much screening would decline, told *HealthDay* that he sees a trend away from "thoughtless" to more focused screening, "with informed decision-making going on between doctor and patient."[6]

Werntz' figures from OHSU showed that PSA testing in new patients 40 years or older declined, from 14% in the years prior to the recommendation to 7% in the years that followed.[1] **EBO**

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Cardiovascular Side Effects of Cancer Treatment Demand Attention

Surabhi Dangi-Garimella, PhD

Chemotherapy and radiotherapy are standard treatment regimens in oncology care. As they undergo therapy, patients experience numerous side effects that can drain them both physically and emotionally, and follow-up care for patients in remission is quite focused on determining if the cancer has returned or progressed to a distant site. However, the increasing survivorship rates among cancer patients has brought a growing awareness of a serious latent impact of chemotherapy and radiation: cardiotoxicity (TABLE 1). Although extensive research has found cardiovascular complications associated with cancer therapy to be responsible for morbidity, and even mortality, among cancer survivors,[1-4] our understanding of the tools for identifying and preventing these complications is limited.

TABLE 1. Late Cardiac Effects of Cancer Treatment

CONDITION	CHARACTERISTICS
Vascular	Atherosclerosis Hypertension Arterial thrombosis Deep venous thrombosis
Structural	Valvular heart disease Pericardial effusion Pericardial constriction Conduction system disease
Myocardial dysfunction and heart failure	

Source: Lenihan DJ, Cardinale DM. Late cardiac effects of cancer treatment. *J Clin Onc*. 2012;30(30):3657-3664.

TABLE 2. Partial List of Institutions That Provide Integrated Cardio-Oncology Care for Cancer Patients

ACADEMIC INSTITUTE/HOSPITAL	PROGRAM
Yale-New Haven Hospital	Smilow Cancer Hospital Cardio-Onclogy Program
Massachusetts General Hospital	Massachusetts General Hospital Cardio-Oncology Program
Dana-Farber Cancer Institute	Cardio-Oncology Program in Collaboration with Brigham and Women's Hospital
Cleveland Clinic	Cardio-Oncology Center
Cedars-Sinai	Cardio-Oncology Program
University of Michigan	University of Michigan Cardiovascular Center Cardio-Oncology Clinic
University of Rochester Medical Center	Cardio-Oncology Program

PREVENTIVE MEASURES

Various pharmacologic and nonpharmacologic approaches are being evaluated to prevent or reduce cardiovascular risk in cancer treatment. These include altering the administration strategies for anthracyclines, administering antioxidants like dexrazoxane, and administering cardiovascular drugs such as ACE inhibitors and beta-blockers.[5] Prophylactic treatment with inhibitors of the renin angiotensin system was recently shown to partially attenuate the cardiotoxicity of doxorubicin and trastuzumab in a mouse model.[6] However, risk stratification using blood-based biomarkers and sophisticated imaging techniques might have the most impact with respect to identifying an appropriate treatment plan to reduce or minimize the cardiovascular effects of these drugs.

Rational drug design—aided by structure activity relationship studies—in the development of newer anticancer agents can also help prevent or reduce cardiovascular side effects. The c-Kit inhibitor imatinib, for example, was redesigned to prevent interaction with Bcr-Abl and JNK proteins, which can limit the agent's cardiotoxic potential.[7]

NEED FOR INTEGRATED CARE

The lessons that have been learned in oncology care, as in all kinds of healthcare, highlight the need for increased communication among the various physicians who contribute along the continuum of care. For a cancer patient, a collaboration between the oncologist and a cardiologist to formulate a multidisciplinary approach to patient care is of the essence—a fact increasingly acknowledged by treating physicians.[8] Management of chemotherapy–related heart failure, prevention of cardiotoxicity by administering cardioprotective agents, cardiac monitoring during chemotherapy, and assessment and prognosis of cardiac risk with respect to a specific chemotherapy regimen are the most commonly observed clinical scenarios that could greatly benefit from an interdisciplinary approach in the management of cancer patients with cardiovascular risk.[8]

Several major cancer centers in the United States (TABLE 2) now boast a cardio-oncology program that includes a team of cardiologists and oncologists who screen patients prior to receiving chemotherapy, and develop treatment plans that would reduce their risk of cardiac side effects.[9]

COST-EFFECTIVENESS OF SCREENING

Collaboration among oncologists, cardiologists, and others who provide care for survivors of pediatric cancer has the potential not just to improve outcomes, but also to curtail costs of care in high-risk patients before the disease becomes debilitating.

A study simulating the impact of an interval-based echocardiography assessment on lifetime risk for systolic congestive heart failure (CHF), lifetime costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) in childhood cancer survivors found a 2.3% to 8.7% reduction in risk for CHF. Further, the ICER for assessment every 10 years was $111,600 per QALY compared with no assessment. Assessment every 5 years yielded an ICER of $117,900 per QALY, while more frequent assessment resulted in ICERs exceeding $165,000 per QALY.[10]

The Children's Oncology Group's (COG's) Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers is a resource for healthcare professionals who provide care to survivors of pediatric malignancies.[11] COG guidelines recommend lifetime echocardiographic screening for asymptomatic left ventricular dysfunction (ASVLD) in childhood cancer survivors who were treated with anthracyclines. Following the guidelines, researchers found, could extend life expectancy by 6 months, increase QALYs by 1.6 months, reduce cumulative incidence of heart failure by 18% (30 years after cancer diagnosis), and have an ICER of $61,500.[12]

PATIENT ENGAGEMENT

The patient can be an active partner in the process, and including the patient in the conversation on long-term care can have a tremendous impact on survival outcomes. The commentary in this issue by Debra Madden, a patient advocate and a 2-time cancer survivor, underscores the importance of an engaged patient (**see cover**).

A collaborative study published in 2013 evaluated whether an educational intervention—in the form of a newsletter—could improve medical follow-up in pediatric cancer survivors who were at increased risk of treatment complications. The study population included survivors—at least 25 years of age—who had participated in the Childhood Cancer Survivor Study and were at increased risk of cardiovascular disease, breast cancer, or osteoporosis related to previous cancer treatment. The study authors designed a newsletter that included either brief health risk information or an insert with more comprehensive risk information. A survey, conducted 2 years following the distribution of the newsletter, evaluated the impact of the intervention on medical follow-up by the survivors.[13]

While the study found no advantage to including detailed information on health risks that the survivors faced, the newsletter increased patient awareness of the risk factors of developing cardiac problems and osteoporosis. This led to an increase in discussions on cancer-related risks with physicians and significantly influenced participation in health screening.[13]

The importance of patient engagement and self-care is coming to be appreciated not just during the care process, but much earlier during drug development. Drug developers, regulators, providers, and health plans are increasingly paying attention to patient-reported symptoms. Organizations have developed strategies to measure and validate patient-reported outcomes, with the aim of improving both the quality of care delivered and health outcomes. As awareness of cardio-oncology issues increases, measures being adopted on multiple fronts can be expected to reduce the cardiac impact of oncology treatment regimens. **EBO**

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PROVIDER COMMENTARY

Importance of a Heart Failure Disease Management Program for Chemotherapy-Induced Toxicity

Anecita Fadol, PhD, RN, FNP, FAANP

Delivering cost-effective, high-value care is a major goal of healthcare institutions across the United States that will continue to dominate healthcare reform in the years ahead. In an effort to control the cost of healthcare, reducing hospital admission rates has become a national priority.[1] Hospital readmission rates, particularly excessive 30-day readmission rates for select diagnoses, are now being closely monitored by CMS, the single largest payer for healthcare services in the United States. The Hospital Readmission Reduction Program, developed by CMS in 2012, assesses financial penalties against hospitals with excess readmissions, and initial efforts have focused on heart failure (HF), acute myocardial infarction, and pneumonia. Excessive readmission rates for patients with these diagnoses are subject to a reimbursement penalty. This has a major impact on the management of cancer patients because a large number (52.8%) of new cancers are diagnosed among Americans 65 years and older, who are therefore treated through Medicare.[2] Although specialty hospitals (ie, some cancer centers) are currently exempted from this initiative, the process of public reporting began back in 2013.

Cancer care has undergone tremendous progress in recent years with the development of effective anticancer therapies, resulting in increased survivorship. However, as several new anticancer agents with cardiovascular side effects entered the therapeutic armamentarium, cardiotoxicity has presented a major challenge and added to the complexity of cancer care. As the population ages, the number of cancer cases will continue to rise at the same time that coronary artery disease starts to manifest. Moreover, multiple comorbidities associated with aging increase the complexity of care, requiring multiple providers and specialists to care for a patient over the course of cancer therapy and creating the risk of fragmented and inefficient care. Several reports have described the fragmentation of care delivery among patients with cancer and a lack of effective communication among multiple providers and specialties involved in patient care.[3-5] Disintegrated care in patients with multiple comorbidities, including the cardiotoxic effects from cancer treatments, can lead to unplanned hospitalizations and visits to the emergency department that could have been avoided.

THE HEART SUCCESS PROGRAM

To promote collaboration and efficiency, we developed an interdisciplinary team–based Heart Success Program (HSP) to coordinate the management of concurrent cardiomyopathy (CMP) and HF while the patient is receiving cancer treatment. The goals of the program are multipronged:

- Develop patient-centered care with active patient involvement in the management of their illness.
- Implement evidence-based pharmacologic therapy for HF based on current clinical guidelines.
- Increase compliance with the CMS core measures for HF.

Through an interdisciplinary team approach, HSP provides a means of communication between the oncology and cardiology teams to streamline work efforts and facilitate the care of patients with cancer and concurrent HF. HSP is an example of implementing the Institute of Medicine (IOM) recommendation as outlined in its report, "Delivering High-Quality Cancer Care," which identified the need to address the complex care needs of persons with multiple coexisting diseases, increased side effects from treatment, and greater need for social support.[5]

The HSP promotes patient-centered care through individualized patient and family education that enables patients to become active "co-managers" of their disease. To ensure patients' understanding of the key points of disease management, nurses reinforce learning through the "teach-back" method[6] while in the hospital, which is reviewed again at discharge.

The HSP promotes patient-centered care through individualized patient and family education that enables patients to become active "co-managers" of their disease.

OUTCOMES

In 2013, a 48-bed medical oncology telemetry unit was selected as a pilot for HSP implementation due to its high volume of HF incidence related to chemotherapy-induced cardiomyopathy. One year following the implementation of the HSP pilot, 112 (6.6%) of the 1702 patients discharged from the unit had a confirmed diagnosis of HF. Of those patients, 98 (87.5%) were discharged alive, while 14 died in the hospital. Of the 98 discharged patients, 41 (41.8%) were re-

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admitted to the hospital within a year. Only 2 patients had hospital readmission for HF exacerbation (one at 19 days and the other at 51 days). The remaining 39 patients were readmitted for reasons other than HF, including fever, pneumonia, anemia, respiratory failure, and chemotherapy-related issues. In addition, a remarkable decrease in 30-day hospital readmissions from any cause was documented—from 37% to 1.02%, before and after implementation of the HSP, respectively.

There was 100% compliance with CMS core measures for evaluation of left ventricular function and initiation of angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin-receptor blocker for patients with left ventricular dysfunction with ejection fraction of <50%. Additionally, there was remarkable improvement in the documentation of discharge instructions—92%, up from 27% documentation compliance at baseline. Published literature has shown that comprehensive discharge planning and post discharge support for patients with HF significantly reduce hospital readmission rates.[7] Even though HF is not a primary medical diagnosis in a cancer hospital, HSP has already laid the groundwork with this quality improvement initiative for cancer patients with HF.

PATIENT SATISFACTION

The patient satisfaction survey scores in the pilot unit have improved from 79.7% (baseline) to 91.7% after the implementation of HSP, particularly in the provision of discharge information. Patient satisfaction with the thoroughness of the staff's discharge instructions and with the information provided about key symptoms has increased by almost 11%. Patient satisfaction was measured by the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey, a standardized tool that allows patients to assess their satisfaction with the care they received during hospitalization.[8] The survey, administered by an independent agency that collects data from patients through mail-in questionnaires after hospital discharge, is focused on 4 main areas: communication with nurses, communication about medicines, care transitions, and discharge information. This instrument allows patients to voice their personal experiences with healthcare while providing meaningful and comparable data to all hospitals. While hospitals can use these patient satisfaction scores for quality improvement, they also increase transparency in the quality of care provided to the general public by different institutions.

An interdisciplinary team approach is needed to avoid fragmentation and inefficiency to deliver cost-effective high-value care.

CONCLUSION

The future of cancer care encompasses a host of novel challenges. It is no longer sufficient to focus exclusively on the cancer diagnosis and associated treatments. Comprehensive cancer care must include preexisting chronic illnesses as well as cancer treatment–related illness and disability. An interdisciplinary team approach is needed to avoid fragmentation and inefficiency and deliver cost-effective high-value care. The novelty of HSP lies in its focus on HF in the context of cancer diagnosis and treatment, and it provides a model for engaging patients and family members as partners with a shared goal of reducing the burden of HF among people with cancer. HSP holds promise for the future creation of similar initiatives aimed at other chronic health problems that affect the overall management of cancer patients. **EBO**

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Extending Cancer Care Past Remission: The Importance of Cardiac Toxicity Monitoring and Awareness

Constantine A. Mantz, MD

In recent years, increasingly effective drug- and radiation-based treatments have contributed to substantial improvements in life expectancy for cancer patients—a finding substantiated not only through my experience as a practicing oncologist, but also in published data.

For example, a 2015 report published in *JAMA Oncology*[1] provided encouraging news of the ongoing efforts against cancer. An analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program of cancers diagnosed and treated between 1990 and 2010 demonstrated significant reductions in the risks of cancer-related deaths from colon, breast, prostate, lung, and liver cancers. Approximately 20% to 60% of those reductions occurred after 1990, and among those populations affected, the largest improvement in survival was observed for patients younger than 65 years.

In other words, there is mounting evidence that physicians, policy makers, and the scientific community are turning the tide in the so-called "War on Cancer." However, despite the encouraging nature of such numbers, these improvements in survival statistics will come at a cost. Indeed, as cancer survivors live longer, treatment-related complications develop into significant concerns for a patient's overall health.

Among the toxicities of cancer treatment, cardiac toxicity is generally the most feared by physicians, as it may erode the gains in life expectancy that result from ever-more effective therapies. Cardiac toxicity has the ability to induce heart failure from treatment-related damage done to the heart muscle—directly or indirectly through promotion of coronary vessel blockage, arrhythmias, elevated blood pressure, and blood clots. Once inflicted, cardiac damage may be irreversible for many patients, and strategies for managing cardiac failure may be temporizing at best. Furthermore, cardiac toxicity due to cancer therapy usually does not manifest itself for years. Despite these potential outcomes, there is currently no standard protocol sanctioned by the American College of Radiation Oncology or the American Society for Radiation Oncology for cardiac follow-up—an oversight that may put the patient at risk.

We at 21st Century Oncology are acutely aware of the pernicious effects of cardiac toxicity, especially as these effects may go undiscovered until it's too late. Therefore, our oncologists preemptively try to identify patients who may be predisposed to severe cardiac damage from cancer treatment, and administer therapies that mitigate the risks of heart failure while still achieving meaningful levels of effectiveness.

CHEMOTHERAPY-INDUCED CARDIOTOXICITY

Common, and generally effective, chemotherapy agents can lead to deterioration of the heart's ability to contract efficiently. In fact, a potentially fatal weakening of the heart was observed in nearly 40% of patients treated at higher doses of chemotherapy associated with congestive heart failure.[2] Additionally, targeted anticancer therapies that inhibit specific molecules within cancer cells and block their ability to multiply

may also adversely affect cardiac cells that express the same target molecule.

With this in mind, we follow a number of processes for the monitoring and management of drug-induced cardiotoxicity, which greatly benefit the patient over the course of treatment—and long past the completion of treatment. Customized to the individual patient's needs, we will order routine initial and follow-up testing of cardiac function; asymptomatic patients demonstrating adverse changes upon routine testing may be directed toward more aggressive medical treatment.

Specifically, patients with known cardiac risks who are scheduled to undergo drug therapy may receive a baseline evaluation of cardiac function through an echocardiogram, followed by regular retesting thereafter. Abnormal test results during therapy may be addressed with drug dose reductions or discontinuation, and abnormal test findings after completion of therapy may be addressed with medical interventions to reduce blood pressure and lipid levels, as well as counseling on smoking cessation and lifestyle modifications.

Medical monitoring and counseling can help us track and contain many harmful effects of cancer drug–induced cardiotoxicity. Patient engagement from the very beginning, along with medically advanced testing methods, can help us surmount cardiotoxicity and better ensure that patients receive only the benefits of essential cancer treatment.

ABOUT THE AUTHOR

21st Century Oncology

CONSTANTINE A. MANTZ, MD

Dr Mantz joined 21st Century Oncology in 2000. He has served in his current capacity as chief medical officer since February 2011 and served as senior vice president of cinical operations from March 2009 to February 2011. Mantz is board certified in radiation oncology by the American Board of Radiology. At 21st Century Oncology, as an area expert, he leads the company's efforts in the study and treatment of prostate and breast cancer.

RADIATION-INDUCED CARDIOTOXICITY

In addition to drug-induced cardiotoxicity, radiation therapy to the breast and chest has been reported as a risk factor for subsequent development of heart disease among long-term cancer survivors. Because of the large number of radiation oncologists in our network and our focus on safety, we also pay particular attention to the effects of radiotherapy-induced cardiotoxicity.

When assessing radiotherapy-induced cardiotoxicity, it is important to consider its unique attributes, many of which are outlined in a *New England Journal of Medicine* report[3]:

- Younger patients with curable cancer treated with radiotherapy to the chest are at highest risk for treatment-related cardiac toxicity.
- Additional factors, such as treatment with chemotherapy or targeted therapies, diabetes, hypertension, and smoking may contribute to the risk of radiation-induced cardiotoxicity.
- The nature of the cardiac injury related to radiation depends upon the extent of cardiac exposure during treatment.

Unfortunately, almost all the reported experiences of cardiac risks following radiation therapy are based on studies that are more than 30 years old, and these involved outdated treatment methods and relatively primitive radiation equipment. Our most powerful tool in combatting radiotherapy-induced cardiotoxicity may prove to be innovation.

Considering cardiotoxicity's almost direct relation to radiation exposure to the heart, it is vital that radiation therapy be precise. Fortunately, more modern methods involve the use of CT scans to accurately define and distinguish the tumor from nearby healthy organs, and sophisticated treatment planning software to design radiation treatment fields that allow for the delivery of effective radiation doses to the tumor while sparing surrounding organs. Furthermore, modern radiotherapy equipment can very precisely shape a treatment field to closely match the size and shape of the tumor while greatly limiting the exposure of tissues just beyond the tumor. This beam-shaping technology is referred to as conformal or intensity-modulated radiation therapy.

Additionally, modern treatment equipment—referred to as image-guided radiation therapy—is capable of capturing an x-ray image of the treatment field prior to each radiation session as verification that organs such as the heart are excluded from exposure as much as possible. Together, these technical improvements allow for greater precision and accuracy in the delivery of radiotherapy and improved sparing of the heart, which could subsequently reduce exposure-related cardiac risks. Put simply, innovation is truly guiding our ability to combat cardiotoxicity.

In order to supplement advances in technology, we at 21st Century also maintain clinical guidelines that provide safe dose limits for our patients' treatment with radiation therapy. This way, we can ensure that no matter the equipment used, patients are receiving safe levels of radiation—something that provides an additional level of security down the road.

Medical monitoring and counseling can help us track and contain many harmful effects of cancer drug-induced cardiotoxicity. Patient engagement from the very beginning, along with medically advanced testing methods, can help us surmount cardiotoxicity.

In the end, even as technology continues to drive us forward in both traditional oncology and radiation oncology, we must never lose sight of cardiotoxicity. Ensuring our patients' health begins at diagnosis, but it must extend into remission. Our duty as oncologists must include attentive follow-up to sustain our patients' health. We must also increase awareness of the risks of cardiotoxicity. As patients battle for their lives—and even after they have beaten back the disease—they do not consider the future effects of their treatments.

In addition to patients, private and public payers are not necessarily aware of the long-term effects—and costs—of cardiotoxicity. Among private payers, claims adjudications resulting from utilization of inappropriately narrow clinical pathways and onerous authorization processes may further inhibit the diagnosis and treatment of such patients. However, all payers share a common concern when it comes to the high costs of avoidable hospitalizations and procedures. Effective risk management of cardiac toxicity due to treatment would help mitigate those costs—an effort that, once again, begins with awareness. Managing cardiotoxicity makes sense from every perspective in our healthcare system. Increased communication among various stakeholders is the call of the hour.

Through coordinated efforts and enhanced patient education, consistent lifelong management of cardiotoxicity is becoming a reality for those in the 21st Century Oncology network. We hope our efforts can serve as a model; more so, further research, improved treatments, and increased collaboration among stakeholders will prove vital in years to come. **EBO**

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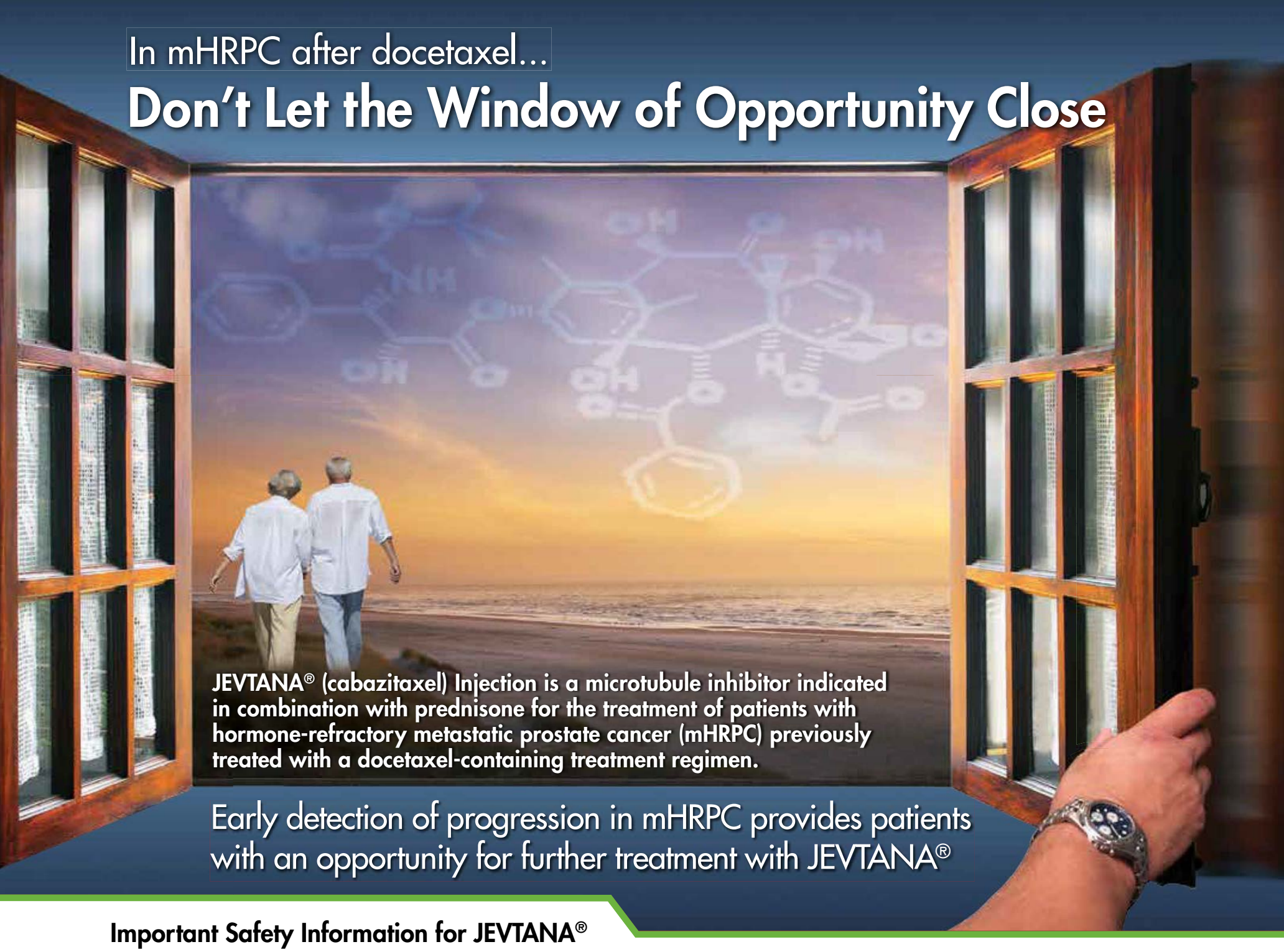
1. Zeng C, Wen W, Morgans AK, Pao W, Shu X, Zheng W. Disparities by race, age, and sex in the improvement of survival for major cancers: results from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program in the United States, 1990 to 2010. *JAMA Oncol*. 2015;1(1):88-96.

2. Bovelli D, Plataniotis G, Roila F; ESMO Guidelines Working Group. Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2010;21(suppl 5):v277-v282.

3. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013;368:987-998.

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**

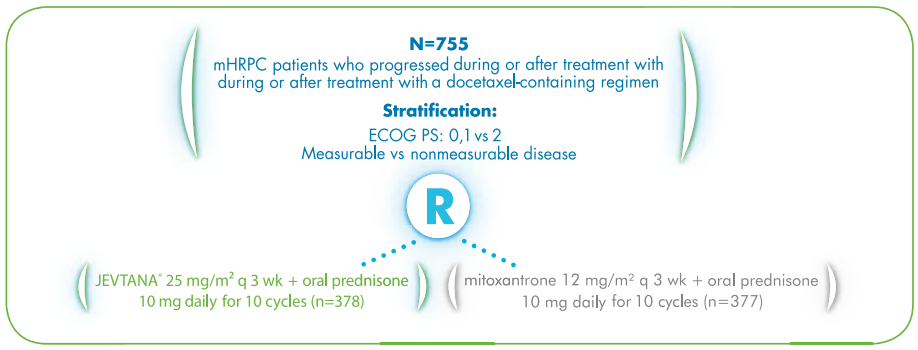
Please see additional Important Safety Information and Brief Summary of Full Prescribing Information, including boxed WARNINGS, on adjacent pages.

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

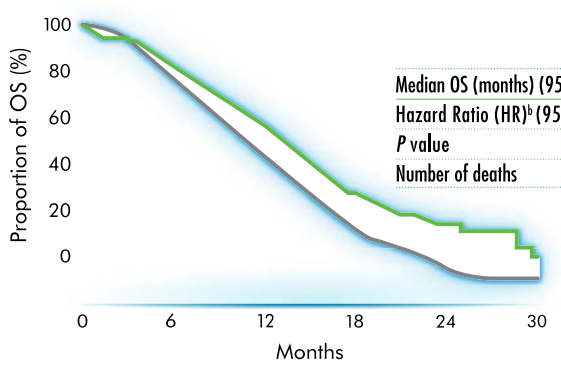
*For measurable disease according to RECIST criteria.
RECIST=Response Evaluation Criteria In Solid Tumors.

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.

References: 1. de Bono JS, Oudard S, Ozguroglu M, et al; for the TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open label trial. Lancet. 2010; 376(9747):1147-1154. **2.** JEVTANA® Prescribing Information. Bridgewater, NJ: sanofi-aventis U.S. LLC; November 2014. **3.** Data on file. Clinical study report (TROPIC). A randomized, open label multicenter study of XRP6258 at 25 mg/m² in combination with prednisone every 3 weeks compared to mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a Taxotere®-containing regimen. Study number EFC6193. sanofi-aventis. March 18, 2010.

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[Þ]	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.

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Influence of Cardiotoxic Risk on Treatment Choice in Adult Cancers

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It is a time of unprecedented therapeutic innovation in oncology. While we still rely heavily on our tried and true therapies for cancer care—prevention, surgery, radiation, and chemotherapy— newer treatments with novel mechanisms of action have expanded our options. In addition, we have better tools to predict risk of recurrence and sequelae of treatment. How we use these tools to treat and cure cancers is the bigger question. Optimal use of the available treatment options to cure disease while facilitating a healthy survival among our patients is our principal goal. Thus, understanding and reducing the risk of long-term sequelae of treatment remains a critical part of treatment planning.

The concept of maximizing efficacy and minimizing toxicity while controlling cost remains fundamental to the triple aim of shifting from volume- to value-based cancer care: improving an individual patient's care quality, reducing per capita costs of treatment, and improving population health. This serves as the framework for the Value Pathways program, and choice of therapeutic agents should be taken in context with each individual patient when making treatment decisions.[1] Because guideline systems are based in large part on clinical trials, and only a select 3% of US cancer patients enroll in prospective clinical trials, oncologists need to make careful decisions about whether certain guideline-based treatments are appropriate for their patients who may on average be older, have more comorbid illness, and therefore, be more likely to experience toxicities related to their disease and its treatment. In addition, further research needs to be conducted with real-world data to better characterize differential toxicity profiles in populations that are underrepresented in these clinical trials and require treatment: the elderly, minorities, individuals who have survived and received treatment for other cancers, and individuals with a heavier burden of comorbidities.

Many agents have been implicated in causing cardiotoxicity, but quantifying how often this toxicity occurs, identifying which patients are more susceptible, and determining the context of risk versus benefit of treatment are all important considerations when deciding the appropriate treatment for a patient. This consideration is different in patients with potentially curable cancers versus patients undergoing chronic treatment for incurable cancers. What is required is not an extensive review of acute and chronic toxicity of systemic treatments in cancer, but rather of how chronic cardiotoxicity risk in cancer therapy impacts treatment choices for our patient. As we often use pathways, guidelines, and clinical trials to guide us in evidence-based treatment decisions, it is important to recognize that these guidelines are created based on results from clinical trials that enroll, on average, younger and healthier patients compared with the average cancer patient who enrolls in trials. In addition, minorities and patients with a history of other cancers have lower rate of enrollment in clinical trials, and thus are underrepresented in these prospective clinical studies that direct pathway and guideline development.

What is required is not an extensive review of acute and chronic toxicity of systemic treatments in cancer, but rather of how chronic cardiotoxicity risk in cancer therapy impacts treatment choices for our patient.

CARDIOTOXICITY AND TREATMENT CHANGE IN PATIENTS TREATED WITH CURATIVE INTENT

Anthracyline-related cardiotoxicity

Anthracylines remain the greatest concern, as they are a common part of chemotherapy regimens administered for curative intent. Their associated cardiotoxicity can be severe and permanent, often resulting in a clinical presentation of heart failure, pathologic evidence of damage to cardiac muscle, and progression to severe heart failure and even death. Chronic anthracycline-related cardiotoxicity is well described and is a dose-dependent phenomenon.[2] Doxorubicin is the anthracycline most frequently associated with cardiac disease, though all anthracyclines pose some risk. While cardiotoxicity is relatively infrequent (1.7%) with cumulative doses of doxorubicin of <300 mg/m^2, other risk factors can increase the incidence of cardiotoxicity even at lower doses of anthracycline exposure.[3] While cumulative dose poses the highest risk for cardiotoxicity, preexisting cardiac disease, hypertension, diabetes, prior chest wall irradiation, older age, and concomitant administration of other potentially cardiotoxic drugs can all increase the possibility of cardiotoxicity.[4]

For patients treated with curative intent, such as in the adjuvant setting for breast cancer, these risk factors may alter chemotherapy regimen choice or dose for the patient. For example, if a patient with early-stage breast cancer requires chemotherapy for risk reduction but has risk factors for chronic anthracycline-related cardiotoxicity, a non-anthracycline choice of chemotherapy may be a more reasonable therapeutic option. The uptake of docetaxel and cyclophosphamide in the adjuvant treatment of breast cancer is an ideal example of the increased utilization of non-anthracycline regimens observed in the last several years.[5] Sometimes, even if a patient has a higher risk of recurrence, the patient's age, prior treatments, and comorbidities increase the risk for complications and deter administration of adjuvant chemotherapy. These are challenging decisions for doctor and patient as they carefully weigh the risk versus benefit of using anthracyclines.

When patients have curable cancers with fewer treatment options, as is the case with some acute leukemias and lymphomas, the benefit of treatment so far outweighs the risk of treatment that the decision is usually made to pursue aggressive therapy despite the risk of adverse complications. In these situations, choices to embark upon aggressive therapy are often balanced with treatment modifications in an attempt to reduce risk. A review of 7 major studies concluded that the risk of cardiotoxicity with anthracyclines was reduced following longer infusion rather than bolus infusion schedules.[6]

This risk reduction, however, was not demonstrated in the pediatric literature—specifically childhood leukemia survivors—where cardiotoxicity was not different between patients who received their anthracyclines in a prolonged infusion versus bolus treatment in a prospective trial.[7] Dexrazoxane has also been used to attempt to prevent cardiotoxicity, but its effectiveness remains unclear, and some studies hint that it could increase the risk of secondary malignancies.[8]

Targeted therapies

Targeted therapies also pose a risk of cardiotoxicity. Trastuzumab is commonly used in the adjuvant setting to treat with curative intent the 20% to 25% of patients with breast cancer who overexpress the epidermal growth factor receptor, HER-2/neu. While trastuzumab is potentially cardiotoxic, it's toxicity is not a dose-dependent phenomenon, and it often manifests with asymptomatic echocardiogram findings of decreased ejection fraction, does not cause permanent damage to the cardiac myocytes, and is often reversible with treatment.[9] Frequently, patients can even be re-challenged with trastuzumab and tolerate it without further toxicity when it is administered after the cardiac function has recovered. While prior exposure to anthracyclines and a history of cardiac disease increase the risk of trastuzumab-related cardiotoxicity, elevated body mass index, hypertension, and diabetes mellitus are not recognized as risk factors.[10]

Combining trastuzumab with anthracyclines can increase the incidence of cardiotoxicity by nearly 27%, but by a much lower amount (13%) when coadministered with paclitaxel.[11] If a patient

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is at risk for cardiotoxicity and is also at high risk for breast cancer recurrence, a risk-versus-benefit consideration is appropriate prior to choosing a therapeutic regimen. For patients who receive trastuzumab in the adjuvant setting, echocardiography is recommended every 12 weeks so that subclinical cardiac dysfunction can be identified early. In the neoadjuvant setting, pertuzumab is now frequently administered with trastuzumab in early-stage breast cancer to provide a complementary mechanism of HER-2 blockade. A meta-analysis observed a low incidence of cardiotoxicity with pertuzumab—a significant decrease in left ventricular ejection fraction in:

- 6.9% of patients treated with pertuzumab alone
- 3.4% of patients treated with pertuzumab in combination with a non-anthracycline cytotoxic therapy
- 6.5% patients treated with pertuzumab in combination with trastuzumab.[12]

CARDIOTOXICITY AND TREATMENT CHANGE IN PATIENTS TREATED WITHOUT CURATIVE INTENT

In patients with incurable cancers, the treatment consideration for administration of agents with risk for cardiotoxicity is different. The risk of treatment in these patients may be greater, as the duration of therapy is often prolonged, the patient may be in poorer health, there may be a greater choice of therapeutic options, and the benefit in terms of risk reduction is usually less. In older patients, patients with reduced performance status, and patients with a heavier burden of comorbid illness, treatment choice should reflect these heightened risks of complications, and dose reduction should be considered. Other agents used in the metastatic setting do not yet have adjuvant indications; for example, in the metastatic setting, alternate drug formulations, such as liposomal doxorubicin, can substantially decrease the risk of cardiotoxicity.

In addition to the targeted therapeutics already mentioned, inhibition of the vascular endothelial growth factor (VEGF) pathway through tyrosine kinase inhibition is associated with cardiotoxicity. As a class, the VEGF-mediated tyrosine kinase inhibitors (TKIs) can have variable effects on cardiac function, and understanding each new agent's potential for cardiotoxicity demands careful review. A meta-analysis of patients receiving TKIs demonstrated an 8-fold increased risk over patients not receiving TKIs for prolongation of the QTc.[13] The TKI sunitinib has been associated with a 4% to 8% rate of congestive heart failure.[14,15] Bevacizumab has also been associated with cardiotoxicity, depending on the combination chemotherapy—cardiac issues have only rarely been reported in colon cancer. When bevacizumab was combined with R-CHOP in the MAIN trial, the rates of heart failure increased significantly, from 7% to 16%.[16] In breast cancer, bevacizumab substantially increased the risk of hypertension and congestive heart failure.[17]

In summary, medication-associated risk of cardiotoxicity is an important consideration in determining treatment choice for all patients, especially those at higher risk for complications. These include the elderly and patients with significant comorbid illness who are underrepresented in the prospective clinical trials that influence pathway and guideline choices. Given the explosion of new therapies in cancer care, the risk of each new therapy must be clearly understood prior to making treatment decisions with patients. Data from clinical trials alone are insufficient tfor this purpose, and real-world evidence from higher-risk populations should be generated to inform these treatment decisions. **EBO**

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ABOUT THE EXPERT

ANJU NOHRIA, MD

Dr Nohria is assistant professor, Harvard Medical School, and a member of the Cardio-Oncology Program—a collaboration between Brigham and Women's Hospital and Dana-Farber Cancer Institute. A cardiologist by training, her area of subspecialty is heart failure and transplantation. Nohria spoke to *Evidence-Based Oncology* on how the Cardio-Oncology Program originated and some of the challenges clinicians face in identifying high-risk patients and monitoring cardiovascular risks.

"For a young patient with a high-grade disease, if they are not going to be alive without the chemotherapy, you have to weigh how bad their cardiac condition is and whether it can be managed medically."

—ANJU NOHRIA, MD

Q: CAN YOU PROVIDE A BRIEF HISTORY OF THE LAUNCHING OF THE CARDIO-ONCOLOGY PROGRAM?

A: Dr Lawrence Shulman, chief of staff at Dana-Farber Cancer Institute, and Dr Kenneth Baughman, who was the head of the cardiovascular Shapiro Center at Brigham, recognized the unmet need and together decided to develop a collaborative program. It was primarily initiated as a survivorship program, looking at late cardiotoxicities in people who had previously been treated with anthracyclines and radiation; during the course of the program, though, we recognized the cardiotoxic effects of novel chemotherapy agents as well. So it evolved into a program that looks at survivorship, cardiotoxic effects of novel agents during treatment, and taking care of patients with concomitant heart disease and cancer.

The cardiotoxic effects of anthracyclines have been known for a while; additionally, patients treated with radiation in the late 1980s or earlier were known to present with late cardiac effects. So they decided that being a big cancer center and cardiology center, we needed a program that evaluates this—it was more of an administrative decision. We were not the first in the nation, though, to monitor cardiac effects of oncology treatment—Memorial Sloan Kettering and MD Anderson have had [cardio-oncology] programs for a while.

Q: WHAT IS KNOWN ABOUT THE NEWER ONCOLOGY AGENTS AND THEIR EFFECT ON THE CARDIOVASCULAR SYSTEM?

A: Several tyrosine kinase inhibitors, especially the ones that inhibit vascular endothelial growth factor, have been shown to cause hypertension. So we manage a lot of patients with concomitant hypertension while they are undergoing chemotherapy with those agents. Some of these agents, for example, sunitinib, used to treat renal cell carcinoma, have been shown in some instances to cause cardiomyopathy and heart failure. Some of the newer agents used in the treatment of chronic myelogenous leukemia have been shown to cause acute vascular events, and we are involved in the care of those patients as well.

With several of the newer agents, we still don't have enough information to predict their cardiovascular effects—a few have targets that are expressed in cardiac as well as cancer cells, which may result in unwanted adverse events.

Q: WHAT IS THE DEMOGRAPHIC OF THE PATIENTS WHO PARTICIPATE IN THE PROGRAM?

A: Older persons or those with preexisting heart conditions or cardiac disease tend to be more susceptible. This is true for late cardiotoxicity as well as for acute cardiotoxicity. For example, a 65-to-70-year-old patient with coronary artery disease will be at a greater risk of developing heart failure. Similarly, very young children, whose organs are still developing, tend to be more susceptible to the cardiotoxic effects of these treatments.

Q: WHAT IS THE DURATION OF PEDIATRIC PATIENT MONITORING POST TREATMENT?

A: We frequently follow pediatric patients for a really long time. At the Perini clinic at Dana-Farber—a survivorship clinic run in concert with Children's Hospital—pediatric cancer survivors are followed well into their 20s and 30s.

Q: WHAT ARE SOME OF THE CARDIOVASCULAR END POINTS MONITORED DURING CHEMOTHERAPY?

A: Depending on what the preclinical data show—either animal studies or phase 1 studies—some of the drugs could be more arrythmogenic or could cause Q_T prolongation; so the patient's EKG [electrocardiogram] would be monitored for arrhythmia or Q_T prolongation. Blood pressure would be monitored in patients administered drugs that cause hypertension. Serial EFs [ejection fractions] would be measured for drugs known to cause cardiomyopathy, such as the HER2 blockers trastuzumab, lapatinib, and pertuzumab. Most patients on these drugs end up getting ECHOs [echocardiograms] every 3 months to examine their EFs.

The oncologic community is definitely more aware and vigilant, especially when there are indications [of cardiotoxicity] from preclinical studies.

Q: WHEN DOES THE CARDIOLOGIST BECOME A PART OF THE CARE TEAM OF A CANCER PATIENT?

A: I get involved when there is a problem; I don't see all cancer patients. I only see high-risk cancer patients or those who develop an issue following treatment.

Patient management then becomes a collaborative process—I'd start the patient on cardiac medication, consult with the oncologist on whether their oncology treatment needs to continue or needs to be held till their cardiac function improves. We'd also discuss whether there's a need to alter their oncology regimen, although the final decision is made by the oncologist. I see the patient as often as is needed. It's a collaborative decision, because for a patient with a high-grade disease, if they are not going to be alive without the chemotherapy, you have to weigh how bad their cardiac condition is and whether it can be managed medically. It's a conversation that depends on who the patient is.

Q: ARE MEDICAL ORGANIZATIONS LIKE THE AMERICAN COLLEGE OF CARDIOLOGY (ACC) OR THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY RAISING AWARENESS OF CARDIO-ONCOLOGY?

A: Several major meetings now include sessions on cardio-oncology; at the recent ACC meeting I was part of a half-day session that was devoted to cardio-oncology (**see cover**). The American Society of Echocardiography has developed independent guidelines on how to monitor patients who have been treated with anthracyclines and trastuzumab.

So although it's still a relatively data-free zone, various organizations are working to raise awareness around this issue. What we are still lacking is a mutually acceptable set of guidelines—collectively developed by cardiologists and oncologists—to prospectively monitor these patients, and this is primarily because of the lack of sufficient data in the field.

Q: HOW AWARE IS THE PHARMACEUTICAL INDUSTRY ABOUT THIS ISSUE, AND WHAT STEPS DO THEY IMPLEMENT TO MANAGE THESE DRUG TOXICITIES?

A: Drug developers are quite aware of the toxicities of chemotherapeutic agents, and they include cardiac event side effects in their adverse event reporting. Several cancer drugs have a rapid approval process because progression-free survival is an acceptable end point in cancer—the criteria for approval of oncologic drugs is different, and sometimes it's about the risk-to-benefit ratio. We have to understand it's a different equation, because you have competing risks from 2 lethal diseases and you have to decide whether the benefit from chemotherapy will outweigh the risk of a concurrent cardiotoxic effect of the drug, which could be manageable.

So in closing, there are several novel oncology regimens being developed that could affect various organs, including the heart. Going forward, the more vigilant we are, the better we can manage these patients so we do not necessarily deprive them of essential cancer therapy. **EBO**

THE AMERICAN JOURNAL OF MANAGED CARE 20

Augmenting the Immune System to Achieve Great Outcomes in Cancer Care

Laura Joszt

During the session "Principles of Immunotherapy" at the National Comprehensive Cancer Network 20th Annual Conference in Hollywood, Florida, March 12-14, 2015, Anthony J. Olszanski, MD, RPh, from the Fox Chase Cancer Center, described the complex interplay between the immune system and cancer.

He began with a basic explanation of the history of immunotherapy, noting how because cancer commonly grows from our cells, the immune system often considers the cancer cells as "self" and does not reject the cancer. Because all cancers result in a genetic defect, then at that point, the immune system is able to differentiate and recognize the antigens being produced by the cancer cells. "So even though tumors are

'self,' they have mutations," Olszanski said. "Those mutations are producing mutated proteins or over-expressing them, which may result in an antigen presenting itself as a non-self antigen." He went on to highlight a recent article in the *New England Journal of Medicine* by Snyder et al[1] reporting on a study which found that melanoma patients with more than 100 mutations had a better survival rate than patients with fewer mutations.

Olszanski also described the immunoediting hypothesis, which explains why cancer progression can vary in patients. There is the illumination phase, in which active immune surveillance recognizes the tumor and eradicates it; the equilibrium phase, during which the cancer does not growing as quickly because there is a balance between tumor progression and the immune system trying to suppress that progression; and finally, the escape mechanism, where either reduced immunogenicity prevents the immune system from finding the cancer effectively or the cancer grows faster than the immune system can suppress it.

"So the immunoediting hypothesis really helps explain how some of our patients seem to do exceedingly well, might get complete remissions, and never come back; other patients seems to have stable disease; and some other patients seem to escape it completely," he explained. He went on to describe some of the immunotherapies currently available that are expanding knowledge of both the immune system and diseases. For instance, he said, PD-1 inhibitors have captured a great deal of attention because they have been widely useful in a variety of cancers (eg, the use of nivolumab in non-Hodgkin lymphoma), bringing about some reduction in the tumor burden of a significant number of patients. In addition, the PD-L1 antibody, MEDI4736, has shown activity in a wide variety of cancers, including pancreatic cancer.

"Can we imagine another therapeutic option for our pancreatic cancer patients who have to go through the chemotherapy that we currently give them today?" he asked. "If immunotherapy works in that patient population, I can say that we've really made some headway against one of the most devastating diseases that we currently have out there." **EBO**

> *"The immunoediting hypothesis really helps explain how some of our patients seem to do exceedingly well, might get complete remissions, and never come back; other patients seem to have stable disease; and some other patients seem to escape it completely."*
>
> —ANTHONY J. OLSZANSKI, MD, RPH

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Defining Value in Cancer Care Treatment

Laura Joszt

Participants in a roundtable discussion on the second day of the National Comprehensive Cancer Network (NCCN) 20th Annual Conference in Hollywood, Florida, March 12-14, 2015, devoted much of the discussion to defining value in cancer care and how it can be incorporated into healthcare decision making. Although the first day of the conference was spent touting the benefits and impact of the NCCN Guidelines, the panelists on the "Value-Based Decision Making at the Bedside" roundtable identified a failure to be explicit about value as the guideline's main downfall.

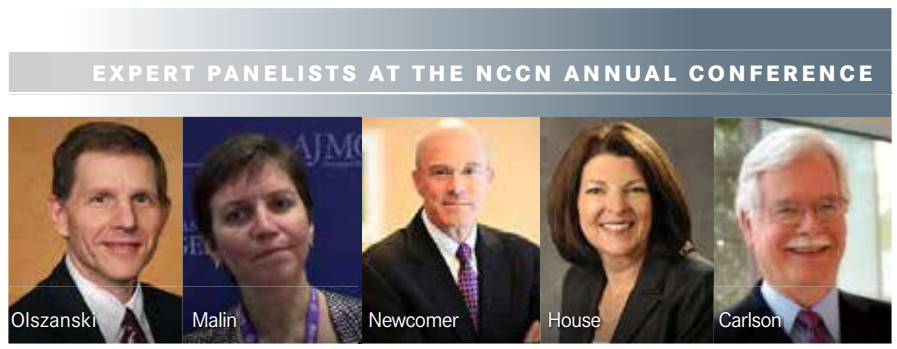
Stephen B. Edge, MD, from Baptist Cancer Center, explained that 80% of patients are treated in concordance with the guidelines, while 20% fall outside of them. Peter Bach, MD, from Memorial Sloan Kettering Cancer Center, is cautious about using the guidelines because they are created from practice medicine rather than evidence and randomized trials.

Linda House, RN, BSN, MSM, president of the Cancer Support Community, expressed this concern with the guidelines: while 60% of patients her organization surveyed said they were aware of guidelines, more than 50% said they did not feel prepared to make their own treatment decisions. "Despite the fact that high numbers say they have received information about their diagnosis and they've received information about potential treatments, [patients] don't really have that level of time and understanding to make an educated decision," she said. "Yet, they're the ones who are living with the long-term effects of it."

Jennifer Malin, MD, staff vice president, clinical strategy, Anthem, and a practicing oncologist, said that she doesn't expect patients to download guidelines and make their own treatment decisions. Instead, the guidelines should be used by clinicians at the bedside to help patients make decisions.

However, Edge explained that while patients can understand their options when clinicians take the time to discuss them, pressures on physicians prevent that from happening.

Further exacerbating the issue is the fact that clinicians cannot explain cost at the bedside. In fact, physicians are largely ignorant about costs, explained James L. Mohler, MD, with the Roswell Park Cancer Institute, adding that he actually doesn't feel qualified to talk to patients about cost. He wasn't alone among the panelists in feeling that discussing cost can be difficult.



Edge agreed that determining cost can be difficult because of the myriad of drug products available on different insurance plans. "You hate to tell someone that it's going to cost $500 and then it turns out it's going to cost $2500," he said. These costs in cancer care have long-term effects. House said that the Cancer Support Community has found that more than 30% of patient families are facing bankruptcy to pay for their cancer care, which can burden patients with excessive levels of guilt while undergoing treatment.

Bach expressed his disbelief that the healthcare industry cannot figure out how much patients are going to pay out of pocket, when a company like Uber can track its cars and let consumers know when to expect them. And yet, a pharmacist can find out how much a patient owes for a prescription in a minute or less. "And for some reason, we don't have [out-of-pocket cost information] at the point of care, and I don't understand why that is," he said. **EBO**

20 Years of Creating and Embracing Guidelines in Cancer Care

Laura Joszt

When the first National Comprehensive Cancer Network (NCCN) Guidelines were developed 20 years ago, even the participating members were skeptical about whether they would be able to come to an agreement and build something lasting, according to some of the people who were there at the beginning.

On the first day of the NCCN 20th Annual Conference in Hollywood, Florida, March 12-14, 2015, panelists took a look back at the last 20 years of the NCCN and why it succeeded when others had failed before. Clifford Goodman, PhD, of The Lewin Group moderated the discussion.

The NCCN was created from 13 academic medical centers that were deeply concerned with then–first lady Hillary Clinton's proposed healthcare plan. Representatives from these centers wanted to make some decisions that would ensure the relevance of their centers when things changed, according to Robert C. Young, MD, president of RCY Medicine. They chose to implement guidelines that would allow their centers and others to measure the quality of the cancer care they were delivering against a set of agreed-upon guidelines. "Unfortunately, fear is a wonderful motivator and that turned out to be the reason why these 13 institutions that compete with one another in some sense got together," Young said.

Both Al B. Benson III, MD, from the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, and Samuel Silver, MD, PhD, assistant dean for research at the University of Michigan Medical School, recalled that the cancer centers could work together. But they found everyone willing to collaborate, and they credited this cooperation to the late Roger J. Winn, MD. "What quickly became apparent with the formation of the panels—and, certainly, the wisdom and efforts of Doctor Winn—it became very clear that panel participation was an enjoyable activity," Benson said. "You were working with your peers, and the discussions were serious and often on target."

Robert Carlson, MD, the current chief executive officer of NCCN, who had been a panel chair at the time of NCCN's inception, agreed that one of the reasons the NCCN succeeded is that it started from a place of collaboration. Coming from a new cancer center that was designated in 2005, Timothy J. Eberlein, MD, of the Siteman Cancer Center at Barnes-Jewish Hospital, explained that as a new arrival it was important to embrace the guidelines, practice the guidelines, and participate in the construction of the guidelines in order to formulate multidisciplinary care.

Lee N. Newcomer, MD, MHA, from UnitedHealthcare, admitted that 20 years ago NCCN and guidelines didn't mean much because payers had seen others come and go, leaving behind 130-page guidelines that were essentially useless. The industry changed its tune, though. "Ten years along, you had a mature product that really did help people if you used it," he said.

According to Dave McFadden, MS, RPh, of Gilead Sciences, Inc, industry quickly realized what these guidelines would mean, namely that if a drug wasn't in the guideline it probably wasn't going to get reimbursed. "The guidelines told us where we needed to generate evidence," he explained. Guidelines have been useful for payers by providing proof to back up their decision not to pay for a drug. It helped that NCCN Guidelines were available for anyone to access and look through and patients and providers could understand that payers' decisions weren't just about saving money, but about the best patient care.

Mary Lou Smith, JD, MBA, cofounder of the Research Advocacy Network, had patients' best interests in mind when she got involved with the NCCN committees as the first patient representative. "The end user of the guidelines is the patient, and therefore that patient should be represented," she said. **EBO**

Session on Cardio-oncology Reflects Growing Number of Survivors

Mary K. Caffrey

ABOUT THE SPEAKERS

ERICA L. MAYER, MD, MPH

Dr Mayer is senior physician and assistant professor of medicine, Harvard Medical School.

LEE JONES, PHD

Dr Jones is associate professor of radiation oncology, Memorial Sloan Kettering Cancer Center.

There was a time when a cancer diagnosis would bring on a single-minded focus on fighting the disease, with little thought to the quality of life afterward. But the sheer number of survivors—nearly 15 million in the United States, or 4% of the population—has brought greater attention to ensuring that cancer treatment does not cause other harms, since cancer patients are not only living but living longer. The National Cancer Institute reports that 41% of cancer survivors live 10 years or more, and 15% live 20 years or more.[1]

After secondary malignancies, cardiovascular (CV) issues are the leading cause of late morbidity and death among cancer survivors.[2] The need for oncologists and cardiologists to be more proactive in developing strategies to work together to prevent heart problems for cancer patients—and later, survivors—was the force behind the half-day Cardio-oncology Intensive, which featured more than 60 presenters and panelists across 6 hours at the 64th Annual Scientific Session of the American College of Cardiology.

The need for collaboration was summed up by Jean-Bertrand Durand, MD, medical director of cardiomyopathy services at MD Anderson Cancer Center in Houston, Texas, who told attendees that to be "fully engaged," every cardiologist should attend at least 1 cancer meeting a year. Bertrand was a coauthor on a 2012 profile of a group of cancer survivors who took part in a Cardiovascular Prevention in Cancer Survivors clinic, which found that the survivors' mean vascular age was 8.4 years older than the mean chronological age.[2] Some of the risk factors those patients faced are well known: three-fourths had received anthracycline chemotherapy, and half had received radiation.[2]

Much can be done, however, in areas of prevention and diagnostics. Early presenters focused on more precise assessment of patient's CV condition before proceeding with chemotherapy, on the use of molecular diagnostics in cancer treatment, which have reduced reliance on antracylcine chemotherapy, and better assessment of a patients CV and lipid profile before cancer therapy begins. Too often, presenters said, patients should have been taking cardioprotective therapies anyway for hypertension or diabetes.

Erica L. Mayer, MD, MPH, a breast oncologist from Dana-Farber Cancer Institute, said many years ago that treating a very young woman with anthracycline for triple-negative breast cancer was a fairly straightforward decision. "It likely had substantial benefit," and probably saved the woman's life, she said.

> *"Oncologists would benefit from more understanding of how biomarkers are changing the diagnostic process on the cardiology side, so that they would make more referrals instead of just ordering an echocardiogram."*
>
> —ERICA L. MAYER, MD, MPH

Fast forward, Mayer said, and if the woman develops a second cancer, now her options are now much more limited. Today, weighing the risk-benefit ratio of cancer treatment with cancer survival offers many more choices, especially in this age of precision medicine. Mayer said that like many other oncologists, she uses the diagnostic test Oncotype Dx to determine which patients would not benefit from certain more toxic therapies, and overall, the use of anthracyline has declined.

When tests offer prognostic and predictive information that the cancer will not respond to chemotherapy, she said, endocrine-based therapy is used instead.

Mayer said, however, that oncologists would benefit from more understanding of how biomarkers are changing the diagnostic process on the cardiology side, so that they would make more referrals instead of just ordering an echocardiogram. It's time, she said, for the oncologist to partner with the cardiologist, "hopefully someone with knowledge of oncology, on how to best co-manage the care."

During a discussion of cardioprotective strategies, exercise physiologist Lee Jones, PhD, of Memorial Sloan Kettering Cancer Center, emphasized the importance of getting an initial assessment of a patient before treatment starts. When he is asked "How much should I exercise during chemo?" the answer is highly personal, because it depends on the patient's activity level and condition before treatment began.

It's not well understood, Jones said, that patients need exercise at different levels of intensity, and some low-intensity exercise is important and beneficial.

In discussing patient cases, presenters noted how often cancer patients arrived with underlying untreated diabetes or hypertension that had to be addressed. Not only do therapies like beta-blockers provide treatment for cardiovascular issues, but some cited research that cancer patients taking beta-blockers had improved survival.

Susan Dent, MD, a medical oncologist from Ottowa, Canada, said there is a great need to grow the evidence base on cardioprotective medications in cancer care. "There's no consensus on what is the best approach," she said. **EBO**

> *"It's not well understood that patients need exercise at different levels of intensity, and some low-intensity exercise is important and beneficial."*
>
> —LEE JONES, PHD

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Preventing Anthracycline-Related Late Cardiac Effects in Childhood Cancer Survivors

Vivian I. Franco, MPH, and Steven E. Lipshultz, MD

BACKGROUND

Treatment advances have extended the lives of children with cancer. Between 2004 and 2010, the survival rate in the United States in children up to 14 years of age with all types of cancer was 83%—significantly higher than the 58% reported in the mid-1970s.[1] Furthermore, between 1970 and 2011, the death rates from cancers diagnosed in children up to 14 years old, and in adolescents 15 to 19 years old, declined by 67% (from 6.3 to 2.1 per 100,000 people) and 58% (from 7.2 to 3.0 per 100,000 people), respectively.[1] However, being cured of cancer is usually not without consequences. Within the first 30 years after diagnosis, survivors of childhood cancers have approximately a 75% cumulative incidence of treatment-related chronic health problems.[2] In the United States, where 1 in 680 people between 20 and 50 years old are survivors of childhood cancer,[3] the impact of long-term health consequences is a cause for concern, and even more so because this population is increasing.

Some commonly used cancer drugs, such as the anthracyclines, are known to be cardiotoxic. Left undetected and untreated, this cardiotoxicity is progressive and persistent and can lead to cardiomyopathy, clinical heart failure, the need for a heart transplant, or death.[4] In fact, 30 years after diagnosis, the number of cardiac-related deaths among survivors exceeds the number caused by cancer recurrence.[5] The prevalence of cardiovascular events, even 5 years after diagnosis, is higher in survivors than in healthy controls (see **FIGURE 1**). In addition, compared with controls, survivors are:

- Fifteen times as likely to have heart failure[2]
- Ten times as likely to have coronary artery disease[2]
- Nine times as likely to have a cerebrovascular event[2]
- Eight times as likely to die from cardiovascular-related disease.[6]

Chemotherapeutic agents may cause adverse cardiac effects either directly, by compromising myocardial structure and function, or indirectly, by impairing vascular hemodynamics or other organ systems such as the endocrine glands, which may result in endocrinopathies. However, pediatric drug toxicity cannot be predicted based on observation of adult patients.[7] While several cardiovascular toxicity studies have been conducted in adult cancer patients, far fewer have been conducted in pediatric cancer patients. Hence, many pediatric treatment protocols are extrapolated from those for adults, which is not always appropriate given the differences in body composition and developmental changes in children. For example, early cardiotoxicity in adults may be lower when anthracyclines are administered as a continuous infusion than as a bolus infusion. However, evidence in children with high-risk acute lymphoblastic leukemia (ALL) indicates that a continuous infusion is not more cardioprotective than a bolus infusion.[8] These results suggest that a continuous infusion in children does not afford incremental oncologic efficacy, but entails the added expense of longer hospital stays and the increased risk of complications, suggesting that continuous infusion of anthracyclines in children for cardioprotection should be contraindicated until evidence to the contrary emerges.

Multiple risk factors for cardiovascular toxicity during and after treatment have been identified. These factors include the cumulative dose of anthracycline, concomitant radiation therapy, younger age at diagnosis, female sex, black race, and the presence of other cardiovascular comorbidities.[9,10] Despite these risk factors, the occurrence of cardiotoxicity remains variable in children, indicative of genetic predisposition.

CARDIOVASCULAR SURVEILLANCE

Monitoring the cardiovascular status of children treated with chemotherapy might detect early cardiotoxicity, even when left ventricular (LV) dysfunction is asymptomatic, thus providing opportunities to prevent, reduce, or treat the condition before it worsens.

Echocardiography is commonly used to monitor cardiac structure and function in anthracycline-treated, long-term survivors of childhood cancer. It is noninvasive, painless, and widely available, and therefore convenient. The Children's Oncology Group has published recommended guidelines for long-term cardiovascular monitoring.[11] Following these guidelines and acting on subsequent abnormal findings could theoretically result in an incremental cost-effectiveness ratio of $61,500, extend life expectancy by 6 months, and improve quality-adjusted life-years by 1.6 months. Additionally, it could, in theory, reduce the cumulative incidence of heart failure by 18% at 30 years after cancer diagnosis.[12]

In contrast, a simulation in which patients were categorized either as low-risk for anthracycline cardiotoxicity (defined by a cumulative anthracycline dose <250 mg/m^2) or high-risk (a cumulative anthracycline dose ≥250 mg/m^2), but were not followed with specific cardiovascular monitoring guidelines,[13] found an overall 18.8% lifetime risk for systolic heart failure in 5-year survivors of childhood cancer aged 15 years, with an average age at onset of 58 years. Further, cardiac assessments and subsequent monitoring-directed treatment every 10 years theoretically reduced the lifetime risk by 2.3%, while a yearly assessment and subsequent treatment reduced the risk by 8.7%—the model predicted incremental cost-effectiveness ratios of $111,600 and $278,600, respectively.[13] These 2 studies illustrate the challenges involvedwith establishing reliable theoretical evidence for such guidelines. Furthermore, the models were restricted to the monitoring of long-term survivors; however, the ability to implement cardiovascular guidelines to predict long-term cardiac outcomes, and biomarker-guided dose modification to improve the overall outcome—defined as the quality of life for a child with cancer and their family over their lifespan—to maximize treatment efficacy and minimize toxicity and late effect outcomes.

Echocardiography, however, lacks the sensitivity and specificity to detect early subclinical abnormalities of LV structure and function in survivors of childhood cancer. Both LV ejection fraction and LV fractional shortening are load-dependent, cannot reliably detect restrictive anthracycline-related cardiomyopathy, and may not identify changes in load-independent LV contractility. Thus, abnormalities in these measurements recorded during therapy may result from causes unrelated to anthracycline-induced myocardial injury.[14]

Newer imaging techniques are being explored but have not been fully adopted by pediatric oncologists, given limited evidence of sensitivity, specificity, and safety in children. For example, Doppler speckle-tracking–derived longitudinal strain echocardiography has been useful in assessing cardiac damage in adults with,[15] and without, cancer,[16] but it has not been studied in children treated with chemotherapy to the point were it could be validated as a surrogate outcome for late cardiotoxicity in long-term survivors.[17,18] Cardiac magnetic resonance imaging may provide quality images of LV function in echo-poor windows, such as in obese patients, but it is expensive, time-consuming, not widely available, it requires a trained physician to interpret the results, and it may require sedating younger patients.[18] In children treated with chemotherapy, there is still no validated method of imaging during therapy for predicting late, clinically important cardiovascular disease. Furthermore, the impact of these newer techniques in routine surveillance, and the optimal timing and cost-effectiveness for such monitoring, requires further investigation.[18,19]

Interest is growing in the use of the serum biomarkers such as cardiac troponin-T (cTnT), cardiac troponin-I (cTnI), and N-terminal pro-brain natriuretic peptide (NT-proBNP), as an additional means of evaluating cardiotox-

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FIGURE 1. Prevalence of Cardiac Conditions Among 14,358 Five-Year Survivors of Cancer, Diagnosed Before Age 21 Years, and a Control Group of Their 3899 Healthy Siblings[6,33]

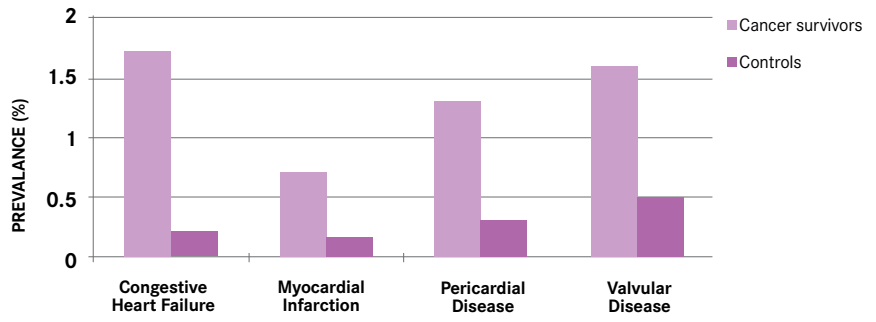

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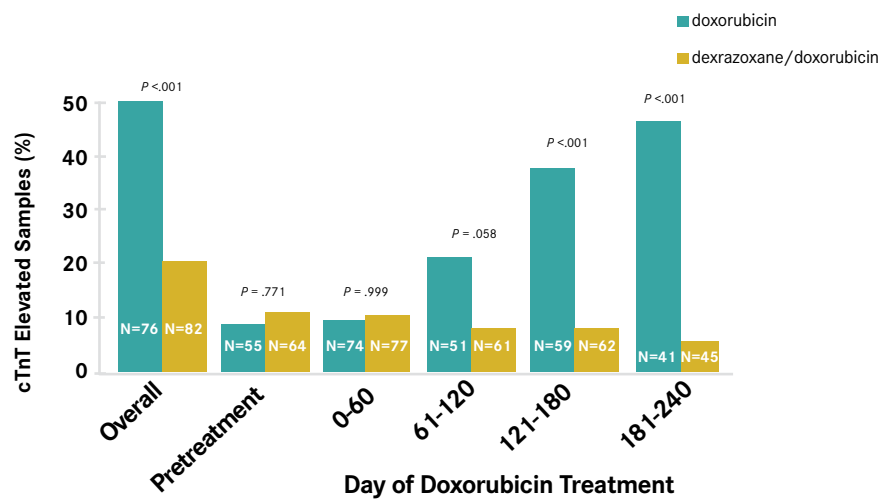
FIGURE 2. Percentage of Children With High-Risk ALL With at Least 1 Elevated Serum Cardiac Troponin T Concentration, Before and During Treatment With Doxorubicin, With Or Without Dexrazoxane[34]



ALL indicates acute lymphoblastic leukemia.
An elevated cardiac troponin T concentration was defined as one exceeding 0.01 ng/mL. The number of patients in whom cardiac troponin T was measured at least once during the specified intervals is shown in each bar.
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icity during and after chemotherapy, is growing. Elevated concentrations of cTnT and cTnI, which are intra-cardiomyocyte contractile proteins detectable in blood after active cardiomyocyte injury or necrosis, generally indicate irreversible cardiomyocyte loss.[20,21] Concentrations of NT-proBNP, a nonspecific marker of ventricular wall stress, can be elevated in several cardiovascular conditions, including cardiomyopathy with increased LV wall stress from pressure or volume overload and heart failure. Increased concentrations of these biomarkers are associated with late adverse cardiac outcomes, as identified by echocardiography, in children receiving anthracyclines for high-risk ALL.[22] For example, elevated cTnT concentrations during the first 90 days of doxorubicin therapy were associated with reduced LV mass and LV end-diastolic posterior wall thickness-to-dimension ratio, a marker of pathologic LV remodeling, 4 years later.[22] Similarly, elevated NT-proBNP concentrations during the first 90 days of therapy were associated with an abnormal LV thickness-dimension ratio, suggesting pathologic LV remodeling, 4 years later.[22] Other cardiac biomarkers indicative of the development or progression of heart failure have not been validated as surrogates of late cardiac status in long-term survivors of childhood cancer treated with anthracyclines.

PREVENTION

Drawing on known or potential risk factors, investigators have studied several methods to reduce the cardiac complications of anthracyclines.[23] Because the most prominent risk factor is the cumulative dose of anthracycline, protocols over the past several decades have tested the efficacy of lower cumulative doses. In the 1970s, before the cardiotoxicity of anthracycline was known, childhood ALL clinical trials would administer cumulative doses of doxorubicin greater than 400 mg/m^2. Several years later, these patients experienced persistent and progressive, clinically important adverse LV effects.[9,24] As a result, subsequent protocols in the 1980s and early 1990s reduced the cumulative doses of anthracycline to 45 to 60 mg/m^2 for children with standard-risk ALL, and to 345 to 360 mg/m^2 for children with high-risk ALL.[25]

Despite a lower risk of cardiotoxicity with the reduced cumulative doses of anthracycline, children with high-risk ALL remained at increased risk for late LV abnormalities.[8,26] In the 1990s, an analysis of 189 long-term survivors of ALL from the Dana-Farber Cancer Institute ALL Consortium and patients treated in Denmark revealed a lower risk of LV abnormalities in survivors who received a cumulative doxorubicin dose of ≤300 mg/m^2 than in those who received >300 mg/m^2 after a median follow-up of 8 years.[27] Thus, the cumulative dose for high-risk ALL protocols from 1995 onward was again reduced to 300 mg/m^2.[25] Although reducing cumulative anthracycline doses may offer some cardioprotection, it may also reduce treatment efficacy.[26] In addition, although doses of ≤300 mg/m^2 reduce the risk of cardiotoxicity, they do not eliminate the risk.[28] Subclinical cardiac abnormalities have been detected at even the smallest doses of anthracyclines (≤100 mg/m^2), almost 10 years after diagnosis.[29] In reality, there is no safe dose of anthracyclines for children with cancer if the goal is to avoid lifetime cardiac abnormalities.

The most promising solution for preventing cardiotoxicity is the coadministration of dexrazoxane. Dexrazoxane is a chelating agent that reduces the formation of anthracycline-iron complexes, thus interfering with iron-mediated free radical generation.[30,31] It also mitigates doxorubicin-induced DNA damage by inhibiting topoisomerase 2-beta.[32] Dexrazoxane is currently approved by the FDA for use in adults with metastatic breast cancer who have received a cumulative dose of 300 mg/m^2 of doxorubicin and who may benefit from continued treatment with an anthracycline. In August 2014, doxorubicin was designated by the FDA as a drug for orphan diseases in children.[33] Studies in children with high-risk cancer have documented the cardioprotective effects of dexrazoxane when administered before each dose of doxorubicin.[33]

Among 206 children with high-risk ALL randomly assigned to receive dexrazoxane before each dose of doxorubicin (dexrazoxane group) or doxorubicin alone, the number of children with elevations in serum cTnT concentrations—from diagnosis to the end of doxorubicin treatment—was lower in the dexrazoxane group than in the doxorubicin-only group (21% vs 50%) (see **FIGURE 2**). However, about 2 months after doxorubicin treatment, LV fractional shortening and contractility were depressed in both treatment groups, which suggests that echocardiographic measurements are not valid surrogates for subclinical myocardial injury in this setting.[34] A follow-up study of this same cohort, 5 years after completing doxorubicin treatment, showed significantly abnormal mean z scores for LV fractional shortening and end-systolic dimension in the doxorubicin-alone group, but not the dexrazoxane group.[28] Left ventricular wall thickness and thickness-to-dimension ratio differed significantly between groups of treated girls. Furthermore, in a planned subgroup analysis after 5 years, girls receiving dexrazoxane had better values than boys for LV end-diastolic thickness-to-dimension ratio (a marker of pathologic LV remodeling) and LV fractional shortening.[28] Similar findings of cardioprotection with dexrazoxane have been reported in other large studies of children treated with doxorubicin for T-cell ALL and lymphoma[35]; in children with osteosarcoma,[36] (C.L. Schwartz, MD, MPH; L.H. Wexler, MD; M. Devidas, PhD, et al. Unpublished results. 2015) whose treatment also included the known cardiotoxic drug, trastuzumab; and in children with osteosarcoma treated with doxorubicin dose escalations up to 600 mg/m^2 cumulative dose. (C.L. Schwartz, MD, MPH; L.H. Wexler, MD; M. Devidas, PhD, et al. Unpublished results. 2015)

Despite favorable evidence that dexrazoxane offers cardioprotection in children who receive anthracyclines as part of their treatment, only 2% of children with acute myeloid leukemia (AML) and ALL in the United States received dexrazoxane in clinical practice between 1999 and 2009.[37] Physicians have been reluctant to use dexrazoxane for fear of increasing the risk of second malignancies or recurrence. However, several large observational studies have found no evidence of such risk. Significant differences have not been found in 5-year event-free survival (77% for the doxorubicin-only group vs 76% for the dexrazoxane group) or in the incidence of secondary malignancies or recurrence.[28,38-40]

CONCLUSIONS

Advances in cancer treatments have brought hope to children with a diagnosis of cancer—a disease once deemed incurable. However, years later, these same treatments can result in a lowering of quality of life, in part due to cardiotoxicity associated with the treatments. Because treatment-induced cardiotoxicity can be pervasive, persistent, and progressive, developing evidence-based surveillance guidelines is important to identify early subclinical abnormalities that, together with validated risk profiles, can help guide

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As investigators continue to search for less cardiotoxic drugs and more effective prevention and treatment strategies, we encourage the use of dexrazoxane in protocols involving anthracycline-based chemotherapy in treating childhood cancers such as AML and high-risk ALL.

treatment to maximize oncologic efficacy and minimize the risk of long-term morbidity.

Substantial evidence indicates that dexrazoxane is a safe and effective cardioprotective drug in children treated with anthracyclines. As investigators continue to search for less cardiotoxic drugs and more effective prevention and treatment strategies, we encourage the use of dexrazoxane in protocols involving anthracycline-based chemotherapy in treating childhood cancers such as AML and high-risk ALL. In fact, dexrazoxane has become part of the standard of care for patients in the Children's Oncology Group and the Dana-Farber Cancer Institute Childhood ALL clinical trials.[33] Most essential of all is that cardiologists and oncologists collaborate to find treatments that balance oncologic efficacy with the risks of cardiotoxicity to maximize the quality of life and survival for long-term survivors of childhood cancer. **EBO**

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Medical World News®

FDA UPDATES

Zarxio Yet to See Light of Day in US Market

Surabhi Dangi-Garimella, PhD

When Sandoz, a Novartis company, acquired FDA approval for Zarxio (filgrastim-sndz)—a biosimilar to Amgen's Neupogen—in March,[1] it drew a fair amount of attention from the pharmaceutical and regulatory observers. Sandoz received praise for its approach and its case presentation to the FDA (the company has nearly a decade of experience marketing biosimilars in the European market).[2]

Now, a US appeals court has blocked Novartis from selling the product, a recombinant granulocyte colony-stimulating factor that can reduce the incidence of infections in cancer patients receiving immunosuppressant regimens.[3] Amgen's request to block Zarxio was granted by the US Court of Appeals for the Federal Circuit in Washington, DC, on May 5, 2015, the result of a lawsuit filed by Amgen in October 2014 accusing Novartis of failing to divulge certain product information required by law. The suit also alleges patent infringement. Oral arguments on the case were scheduled for June 3, 2015,[3] but no decisions were made.

Zarxio's approval comes subsequent to passage of the Biologics Price Competition and Innovation Act of 2009, a provision of the Affordable Care Act, which recommended the creation of an abbreviated approval path for biosimilars to improve access to innovative products.[4] The case has generated tremendous interest in the field, as its outcome will set a precedent expected to impact the numerous biosimilar products currently under development. These products could be less expensive and can be interchanged with an FDA-approved biological product. A survey by the RAND Corporation estimated that biosimilars would save the United States approximately $44.2 billion over a 10-year period.[5] **EBO**

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Nivolumab Assigned Priority Review for First-Line in Melanoma

Surabhi Dangi-Garimella, PhD

The PD-1 inhibitor nivolumab (Opdivo), developed by Bristol-Myers Squibb (BMS), has been assigned a priority review by the FDA for use in treatment-naïve patients with advanced melanoma. The drug first passed the FDA's scrutiny in December 2014, becoming the second immuno-oncology agent from BMS to do so, when it was approved for patients with advanced melanoma who had progressed on ipilimumab (Yervoy) and a B-Raf inhibitor if they harbored the BRaf V600 mutation.[1]

To support the application, BMS has submitted phase 3 results from the CheckMate-066 trial, in which the performance of treatment-naïve advanced melanoma patients (with wild type Braf) on nivolumab was compared with that of patients on dacarbazine chemotherapy. Treatment with nivolumab improved overall survival (OS) by 58% and progression free survival (PFS) by 57% compared with dacarbazine. There were indications of a biomarker-based response—PD-L1–positive patients had a 70% improvement in OS, while the objective response rate was 52.7% with nivolumab versus 10.8% for dacarbazine.[2]

"The CheckMate-066 trial marked the first time that a PD-1 immune checkpoint inhibitor showed a survival benefit in a randomized phase 3 trial," said Michael Giordano, BMS senior vice president and head of development, oncology .[1]

According to the compamny's website, the FDA is required to act by August 27, 2015. **EBO**

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MANAGED CARE UPDATES

IMS Health Report Estimates $100-Billion Global Cancer Spend in 2014

Surabhi Dangi-Garimella, PhD

In early May, the IMS Institute for Healthcare Informatics released a report, "Developments in Cancer Treatments, Market Dynamics, Patient Access and Value: Global Oncology Trend Report," which estimated that the global cancer spending in the year 2014 crossed the $100-billion mark. This number does not consider discounts or rebates for private and federal payers, or patient access programs.[1]

The analysis found a 6.5% increase in the compound annual growth rate (CAGR) during the 5-year period leading up to 2014, with the United States and 5 European nations the key spenders, accounting for 66% of the total market. Although targeted therapies accounted for 14.6% of the CAGR over the 5-year period, nationalized health systems as well as private payers were cautious and much more stringent in determining who could qualify to receive these treatments, and their cost-effectiveness and value analyses resulted in restricted patient access.[1]

Some of the important findings of this report include:

1. Improved clinical outcomes. Several factors including early diagnosis, better treatments, and longer follow-up may be responsible for improved outcomes. New treatments such as immuno-oncologics, smarter combination therapies to target multiple tumor pathways, and biomarker-based treatment are driving these results.

2. Increased patient awareness through social networks. Better-networked patients are more aware and involved in self-care, resulting in open conversations on treatment options and financial concerns.

3. Patient access to oncology drugs varies across markets. Emerging markets have been slower to accept targeted therapies. Additionally, the more expensive specialty drugs may face access barriers even in wealthy nations, especially if payers refuse to reimburse. Over a 10-year period, treatment costs in the United States have increased by 39%,

patient response rates have improved by 42%, and treatment duration has increased by 45% (reflecting improved rates of survival). At the same time, out of pocket costs have increased sharply (by 71%) for infusions over a 1-year period from 2012 to 2013 among patients in the United States. **EBO**

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Medical World News®

MANAGED CARE UPDATES

CMS Unveils Massive Overhaul to Medicaid Managed Care

Mary K. Caffrey

Rating systems for Medicaid managed care plans and protections that make it easier for consumers to move between Medicaid and qualified health plans as their circumstances change are just 2 elements of the massive proposal unveiled recently by CMS, which seeks to update rules for the first time since 2002.

Andy Slavitt, acting administrator for CMS, said the proposal's 3 main aims are to improve transparency and consumer protections, provide better care coordination, and allow states to pursue delivery system reforms that are well under way in Medicare Advantage and in commercial

insurance. "A lot has changed in terms of best practices and the delivery of important health services in the managed care field over the last decade," he said.

Overall, the proposed rule seeks to bring Medicaid managed care in line with the goals for value-based reimbursement outlined earlier this year by US Secretary Sylvia Mathews Burwell, who has stated that 50% of Medicare reimbursements will be value-based by 2018. But Slavitt emphasized that the proposal gives states the flexibility to tailor Medicaid managed care based on local conditions, and that he was "excited to allow states to have continued room for innovation."

Vikki Wachino, CMS deputy administrator/director of the Center for Medicaid and CHIP Services, filled in details during a briefing with reporters. Among the highlights:

- Rules will allow managed care contractors to communicate more effectively with clients whose incomes are declining and will be transitioning to Medicaid.
- A rating system will be developed to evaluate the quality of plans, but CMS will seek input on whether the system should resemble the "Star" ratings in Medicare Advantage or some other system.

• A number of proposals seek to update the advance of technology since 2002.

CMS reports that more than half of all beneficiaries receive some or all of their care through managed care organizations. A year-end review in 2014 by the Kaiser Family Foundation found that some form of Medicaid managed care existed in 39 states, with varying levels of penetration.

Since the last update, the Internet has become a cornerstone of communication for almost everything, and even the very poor are likely to have smartphones, which many have in lieu of land lines. Consumer advocates have decried the lack of requirements for doctors' directories and other essential pieces of information to be updated continuously online. Consumers and doctors themselves routinely complain about out-of-date lists that limit the ability of Medicaid clients to find a primary care physician, much less specialists.

In a statement, the National Association of Medicaid Directors pledged to work with CMS to ensure ongoing flexibility and innovation. "In many states, Medicaid managed care has become an important tool in transforming a fragmented health care system that pays based on volume into a patient-centered,

coordinated model of care that pays based on value. While some states now have decades of experience in Medicaid managed care arrangements, the industry is still evolving in many ways. Therefore, oversight at both the state and federal levels is vitally important to ensuring these goals," the statement said.

Three words in the proposal have drawn insurers' attention: medical loss ratio. This calculation, known as the MLR, dictates how much of the premium that is collected must be spent on actual healthcare and not administrative costs.

America's Health Insurance Plans (AHIP), the giant trade organization representing insurers, announced through its interim CEO that it was pleased with the overall commitment to flexibility in the rule, but the MLR provision was singled out. "An arbitrary cap on health plans' administrative costs could undermine many of the critical services—beyond medical care—that make a difference in improving health outcomes for beneficiaries, such as transportation to and from appointments, social services, and more," interim AHIP CEO Dan Durham said in a statement. **EBO**

Experts Discuss Medicare's New Oncology Care Model

Surabhi Dangi-Garimella, PhD

The CMS Innovation center (CMMI) recently announced the development of a new payment and delivery model to improve the effectiveness and efficiency of specialty healthcare. The new Oncology Care Model (OCM)[1]—one of several models being developed by CMMI—requires participating physician practices that administer chemotherapy to enter into payment agreements with CMS to measure financial and performance accountability for episodes of care. Incentives in OCM include a monthly per beneficiary-per month (PBPM) payment of $160 for the entire duration of the episode, along with the possibility of a performance-based payment to foster quality care at a lower cost during the episode. CMS hopes to encourage participation by private payers, which would allow for a multipayer model to incentivize care transformation at the physician practices.

From left, Michael Kolodziej, MD; Brian Kiss, MD; Bruce Feinberg, DO; Scott Gottlieb, MD; and Ted Okon, MBA.

To discuss OCM and other issues in oncology care, *The American Journal of Managed Care* conducted the Oncology Stakeholders Summit, Spring 2015 Peer Exchange. From community oncology, to health policy, to health plans, the Summit brought diverse expertise together. The moderator of the panel, Bruce Feinberg, DO, vice president and chief medical officer of Cardinal Health Specialty Solutions, was joined by Scott Gottlieb, MD, resident fellow at the American Enterprise Institute (AEI); Brian Kiss, MD, vice president of healthcare transformation at Blue Cross Blue Shield (BCBS) of Florida; Michael Kolodziej, national medical director for oncology strategy at Aetna; and Ted Okon, MBA, executive director of Community Oncology Alliance (COA). Gottlieb, currently at AEI, has performed various roles at the FDA, including deputy commissioner for medical and scientific affairs, and has also served as a senior policy advisor for CMS.

Feinberg started the discussion on the OCM with the suggestion that in asking private payers to participate, Medicare shows that it expects wider adoption of the model by clinical practices. In Feinberg's opinion, payers, who want to experiment with bundled payment, episode of care, or value-based reimbursement models, might find it easier to do so when they partner with Medicare. He then asked Okon whether he saw similarities between COA's Oncology Medical Home (OMH) model and OCM, and what he might see as the advantage of a collaboration between private payers and CMS on this front.

Okon believes that both OMH and OCM are steps in the right direction; they have similarities because they are both based on a care coordination fee and shared savings. However, noting that the 6-month bundle in the Medicare OCM is diametrically opposite of the premise of shared savings, he added, "It's quite ironic, too, because one of the biggest problems with the accountable care organization (ACO) model, that has been realized now after 2 or 3 years, is it was built on game sharing. So, basically, practices that are doing well in an ACO or ACOs that are doing well all of a sudden find out they can't do any better because they've corrected the problem." With OCM, Okon said, CMS intends to turn around low-performing practices, and involving private payers in the mix would indeed help. But he is absolutely against the long list of measures that both payers and providers had to submit through the letter of intent (LOI) for participation.

Kiss agreed, adding that while BCBS of Florida has been one of the pioneers with oncology payment models, his organization backed off from participating in the OCM after considering the administrative burdens and the associated costs that these measures would transfer to smaller physician and community practices. "We're doing our things independently; that's one of the things we've been successful with early on as a payer, largely because we avoided some of the CMS reporting requirements and we're able to work collaboratively with systems, taking into account the realities of administrating everything we want to do."

Gottlieb took a step back and provided his hypothesis on the broader impact of these measures. According to him, increased administrative burdens are a major driver of the consolidation of smaller, community-based practices with hospitals. He also thinks there may be a migration of physicians—especially with the passage of the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA), which repealed the Sustainable Growth Rate formula—to managed care plans like the Medicare Advantage Plan, which can reduce their administrative burden that entails a fee-for-service Medicare plan. However, Gottlieb thinks this may not impact oncology as much, which sees a higher proportion of Medicare patients.

Okon emphasized the lack of measurements in the CMMI programs being floated. "You don't know the measurements, so how can you possibly turn around and do the things you need to do in your practice from a process standpoint, when you don't have a good idea of where you stand?" he said. To add to this complication, Gottlieb said, the requirements constantly change, which makes it even more difficult for healthcare systems to adapt and improve.

Okon added that the feedback received is much too delayed to implement any changes. On the other hand, he applauded the UnitedHealthcare model, which "brought the practices together and they knew exactly how they were going to be measured, they knew what the starting measurement was, and they got regular feedback."

Kolodziej thinks that while the OCM model is too prescriptive, it has initiated discussions on the concept of transforming healthcare delivery and making physicians accountable for delivering a certain quality of care. Kolodziej said that he's developing oncology medical home relations with several practices, and also with integrated medical centers, the goal being to inculcate such concepts as continuous quality improvement, performance measurement, and considering the patient experience. However, he pointed out, after you develop all these performance metrics, there's no assurance that practices will be reimbursed for it all. So he has developed a much simpler model, but does not know whether CMMI will let him run his model through its program.

Indicating that one of the reasons everyone thinks CMMI delayed its LOI deadline by 2 weeks was that payers were wary of coming on board, Kolodziej provided the flip side scenario—he said practices are only signing up to participate in the OCM because of the PBPM for the 6-month period. "That's not the right way of doing things," he added, because newer practices may either lose money or just break even, while more established practices may earn some profit. And the way the model is currently structured, "They say it's a 5-year model, but built within that is [that] at the 3-year point, if you haven't [generated] any savings, you're out," Kolodziej said.

Both Okon and Kolodziej agreed that CMMI cannot have a global prescription for all clinics. "It's like what Scott said. Healthcare is local," said Kolodziej, and he concluded that while bigger practices can adapt to the OCM, smaller practices just cannot. **EBO**

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Value of Patient-Reported Outcomes in Oncology Care

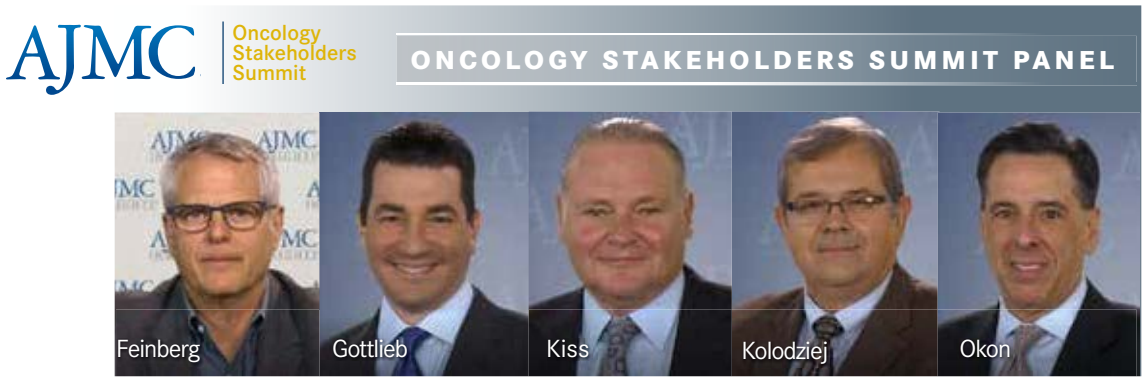
Surabhi Dangi-Garimella, PhD

With the increasing success of oncology regimens in extending overall survival, quality-of-life discussions are making their way into oncology care. Defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else,"[1] patient-reported outcomes (PROs) regarding symptoms, quality of life, and functional status are now routinely being measured in clinical trials.[2] PROs also provide a big boost to the movement toward a patient-centered approach in medicine, and may influence regulatory and reimbursement decisions in oncology.

However, several questions remain—and opinions vary—on the collection of PRO data. To discuss some of these questions, *The American Journal of Managed Care* convened a panel of healthcare experts to participate in the Oncology Stakeholders Summit, Spring 2015 Peer Exchange. The moderator of the panel, Bruce Feinberg, MD, vice president and chief medical officer of Cardinal Health Specialty Solutions, was joined by Scott Gottlieb, MD, resident fellow at the American Enterprise Institute; Brian Kiss, MD, vice president of Healthcare Transformation at Blue Cross Blue Shield of Florida; Michael Kolodziej, national medical director for Oncology Strategy at Aetna; and Ted Okon, MBA, executive director of Community Oncology Alliance. These experts' diverse backgrounds enabled each to bring a unique perspective to the table.

Feinberg opened the discussion by asking each panelist to provide his definition of patient-centered medicine, because "There seems to be a lot of miscommunication or a misperception about what patient-centered medicine really means to different stakeholder groups." According to Kiss, while patient-centered is an overused term, it has revolutionized the American healthcare system by placing the patient front and center. Traditionally, he said, the healthcare system in the United States—fragmented, despite being of high quality—tried to fit the patient into an existing framework of care. "What the patient-centered concept really does is begin to look at the patient, and then create a system that meets their needs," he added. Drawing a parallel to personalized medicine, Kiss emphasized the importance of the healthcare system recognizing patient needs and adapting accordingly.

Gottlieb, who has worked at CMS and also with the FDA, said that payment reform would have a tremendous influence on this way of thinking, to the extent that he predicts that reimbursement will be driven by objective measures in the clinic. He pointed out, though, that CMS struggles with identifying measures for outcomes or quality of care delivered, compared with gathering patient data through surveys and patient-reported outcomes. Pay-for-performance, in his view, will be influenced by information on patient experience with the healthcare setting.



Kolodziej appreciates the change from provider-centric to more patient-centric and welcomes the move to incorporate accountability in the healthcare system with respect to patient experience and outcomes. In his vision, the impact of this changing outlook in the healthcare system will radiate out beyond reimbursement policies and influence both innovation and accountability in healthcare. He pointed out that a substantial evidence base has shown that physician assessment is not a good surrogate for a patient's actual performance. Although the healthcare system has not yet operationalized the tools for shared decision making, he thinks this will happen soon.

Feinberg argued that the healthcare culture usually disregards what the patient wants, leading Okon to echo Kolodziej's thoughts on the need for changing the current culture. Pointing out the important role played by the oncology nurse, he suggested that the processes within a practice should converge on the patient, who should be the focus instead of the physician.

In terms of the day-to-day working of a clinic becoming patient-centered, Gottlieb thinks, the current survey tools in the clinic are far from ideal, making the developing of specific tools to capture the patient experience with treatment and treatment outcomes vital. This, he indicated, is a need to which even the FDA is actively paying attention, with the goal of potentially including PROs in drug labels, he said.

How would the patient feedback gathered by these tools influence reimbursement? According to Kiss, PROs are a healthcare quality measure that needs enrichment to be effectively quantified and connected to outcomes in order to assess technical quality, interpersonal quality, and efficiency of care delivery. Okon added that some of these measures are being tested through the patient-centered medical home model. Citing the example of the Come Home project, headed by Barbara McAneny, MD, he explained that the 7 practices participating in the project have adopted several changes, such as building a function for a nurse navigator throughout the practice and incorporating 19 measures of quality and value into the electronic medical record. "So there are a bunch of other things, but what's really fascinating about this is, a sea change is actually being implemented right now on a real basis."

Gottlieb believes that while reimbursement will be tied to measures established in the clinical setting, it may be harder for government agencies to adopt them; patient experience and PROs, he said, would be much easier to implement. The panel agreed that, probably because of the bureaucracy involved, government agencies have a much harder time than payers in assimilating and analyzing data, and then use it to implement changes in the clinical setting. Gottlieb, based on his experience at CMS, mentioned that it was hard to follow an episode-based payment model because of the difficulty in keeping track of the services a patient would utilize.

Added Kolodziej, "The other thing is, you don't even have to go to an episode model, because in an episode model there are winners and there are really big losers. You can actually do benefit design or network design" to achieve the ultimate objective of high-quality care, which he said can be achieved through narrow networks—easier for private payers to do.

And how about the regulatory aspect of incorporating PROs in drug labels? Gottlieb acknowledged that while the agency could have a tremendous impact on facilitating the process, there is concern about PROs potentiating excessive use, and the worry that patients might overemphasize quality-of-life claims over efficacy claims. While the current FDA guidance[3] is primarily for the pharmaceutical industry—to support their efforts to incorporate PROs into labels—there have been additional public efforts to identify the right measures.

"The whole thing about patient reported outcomes is really an attempt to identify what it's going to cost the patient," said Kolodziej. "I think what's much more likely is that [PROs] will be part of shared decision making, because although there may not be a best way to do things, I guarantee you there's a worst way to do things, and, to the extent that we can avoid that, everybody benefits."

To view the discussion, please visit http://www.ajmc.com/peer-exchange/oncology-stakeholder-summit-spring-2015/Introduction-Patient-Centered-Care-in-Oncology. **EBO**

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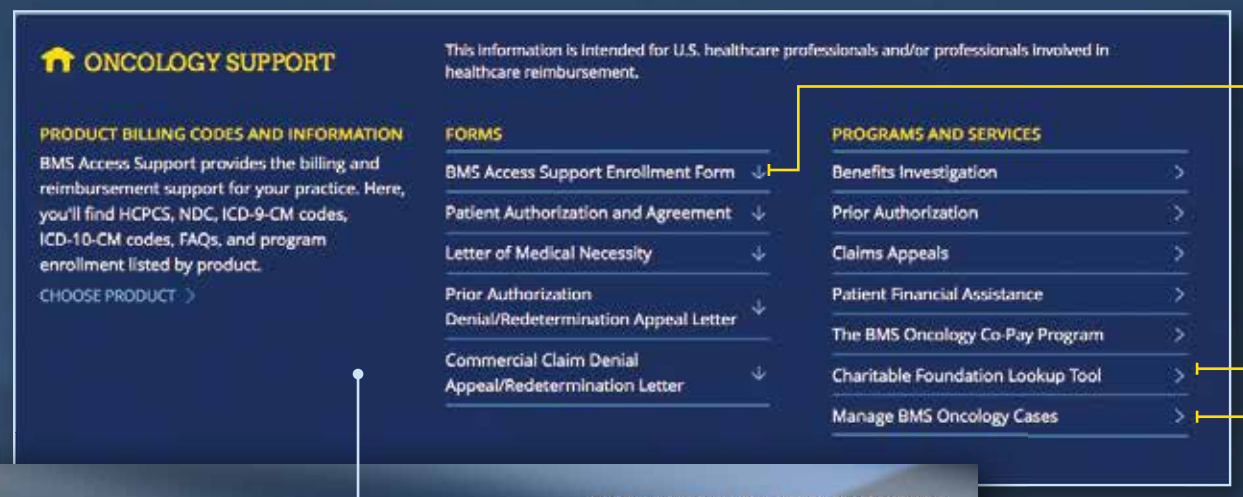

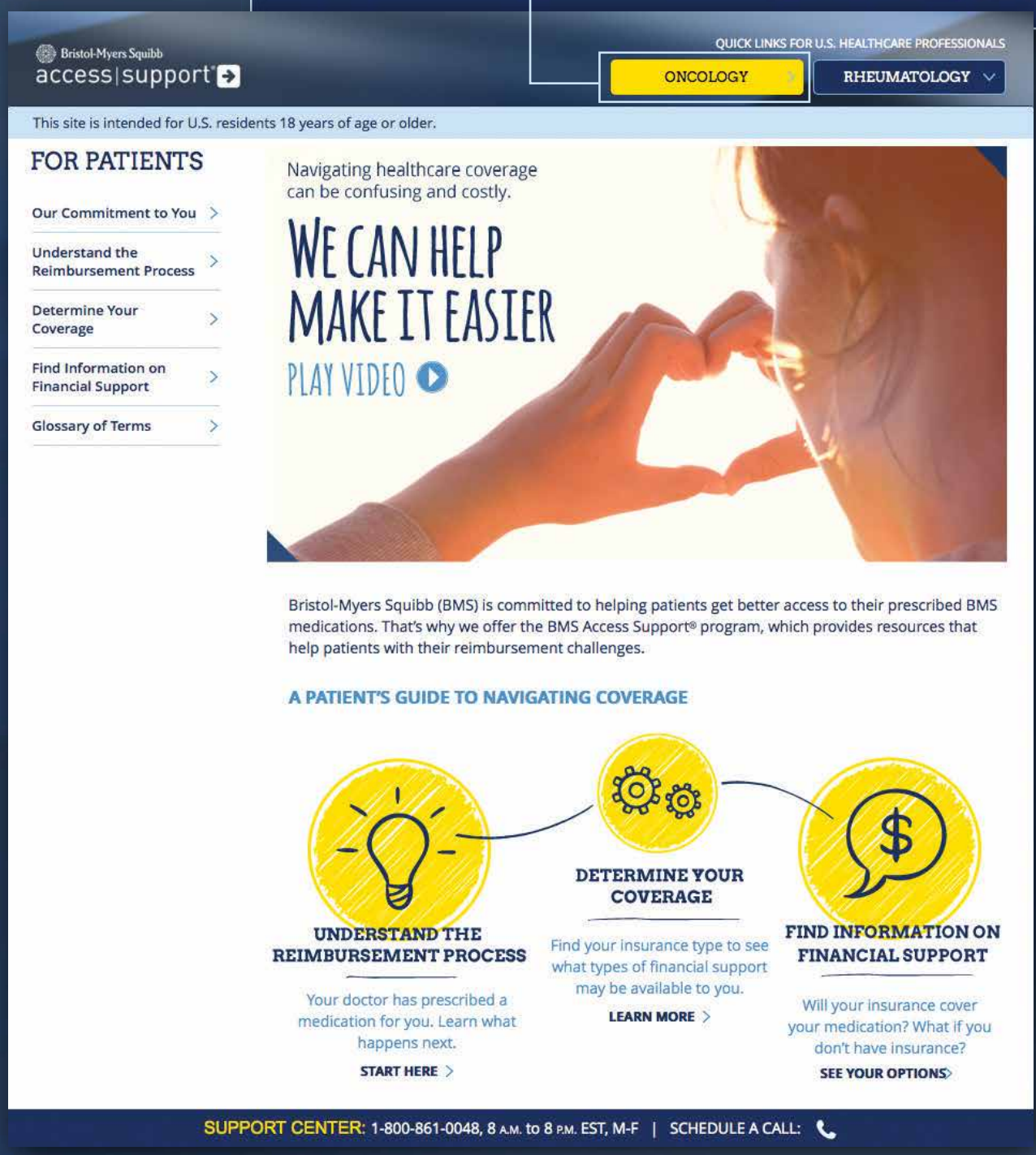

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Cardio-Oncology: The Intersection Between Cancer and Cardiovascular Disease
(CONTINUED FROM COVER)

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Tomas G. Neilan, MD, assistant professor of medicine, Harvard Medical School, co-director, Cardiac MR PET CT Program, Massachusetts General Hospital.
Aarti Asnani, MD, (Joining the Program in July as an instructor in medicine.)

The potential cardiotoxicities include hypertension, cardiomyopathy, QT prolongation, arrhythmias, thrombosis, and metabolic abnormalities. It is important to note that the cardiovascular profile is different for each drug.

For many cancers, including breast cancer and lymphoma, chest radiation remains an important component of the treatment regimen. The cardiovascular risks of radiotherapy include coronary artery disease, valvular heart disease, pericardial disease, conduction system abnormalities, and myocardial fibrosis.[4] A recent analysis by Darby et al suggested a linear increase in the incidence of ischemic heart disease with higher estimated radiation doses to the heart.[5] The development and validation of approaches to minimize this long-term risk is the focus of ongoing research.

Prompt recognition and management of cardiotoxicity during chemotherapy is critical in order to ensure that patients can continue to receive these important treatments. There are data suggesting that early recognition of chemotherapy-induced cardiomyopathy and prompt initiation of medical therapy can promote recovery of cardiac function.[6] Trials are being conducted to validate this approach and define the appropriate method of screening for cardiotoxicity, including the use of cardiac imaging and biomarkers. The development of cardiotoxicity may also increase the risk of morbidity and mortality, as evidenced by an analysis of Medicare patients undergoing treatment for breast cancer.[7] The interplay and balance between the competing morbidity and mortality of cardiovascular disease and cancer is particularly important in an older population, whose risks are inherently higher.

MGH CARDIO-ONCOLOGY PROGRAM

The MGH Cardio-Oncology Program—introduced in 2011—is a joint initiative between the Heart and Cancer Centers at Massachusetts General Hospital that provides comprehensive cardiovascular care to cancer patients, with the goal of improving short- and long-term outcomes (see **FIGURE**).

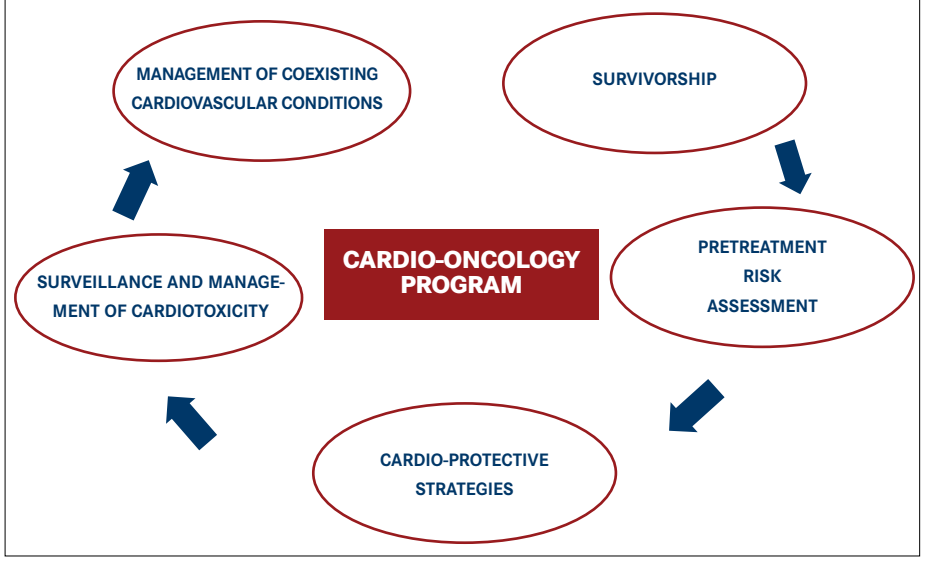
Risk Assessment Prior to Cancer Treatment

For many patients, determining if there are cardiovascular risks that need to be addressed—before they undergo medical or surgical treatments for cancer—is necessary in order to ensure optimal outcomes. Working closely with the cancer care team, we provide a comprehensive cardiovascular evaluation and treatment plan prior to cancer therapy to minimize cardiovascular complications. When appropriate, this evaluation may include diagnostic testing and medical therapy.

Care for Cancer Patients With Existing Cardiovascular Disease

Management of preexisting conditions such as hypertension, coronary artery disease, congestive heart failure, heart valve disease, and arrhythmias in cancer patients requires an approach customized to their overall care. Our goal is to manage existing cardiac conditions so that patients get the best cancer care possible. Adjustment of antiplatelet and anticoagulation therapy may be necessary, depending on bleeding risks during chemotherapy. Additionally, drug-drug interactions may require adjustment of cardiovascular medications during chemotherapy.

FIGURE. MGH Cardio-Oncology Program: Providing Comprehensive Cardiovascular Care for the Cancer Patient Throughout the Disease Continuum



MGH indicates Massachusetts General Hospital.

Monitoring for Cardiac Complications From Cancer Therapy

Patients who are actively receiving chemotherapy or who previously completed chemotherapy and/or radiation therapy may be at an increased risk of coronary artery disease, congestive heart failure, valvular heart disease, pericardial disease, and arrhythmias. Recommendations from groups such as the Children's Oncology Group,[8] National Comprehensive Cancer Network,[9] and a joint committee from the European Association of Cardiovascular Imaging/American Society of Echocardiography are helpful in addressing these concerns.[10,11] There is a limited evidence base to guide many of these recommendations, and future trials will be necessary to validate the comparative effectiveness of these strategies. In the interim, it is important for clinicians and patients to understand the role of surveillance for subclinical cardiotoxicity.

Assessment of Long-Term Cardiac Risk in Cancer Survivors

Owing to increasing evidence that survivors of cancer face higher risks of cardiovascular disease, we provide comprehensive risk assessment and discuss strategies to reduce the risk, including dietary and lifestyle modifications and, when appropriate, medical therapy. Our long-term cancer survivorship program is focused on maintaining optimal cardiovascular health.

Evaluation of Cardiac Tumors

Cardiac tumors are relatively rare and require specialized care. Our state-of-the-art imaging technology to evaluate cardiac tumors includes echocardiography (with 3D imaging), cardiac CT, cardiac MRI, and positron emission tomography (PET). We work closely with colleagues in oncology, radiation oncology, radiology, interventional cardiology, and cardiothoracic surgery to develop and implement a treatment plan for these complex cases.

Assessment of New Chemotherapies

Many chemotherapeutic agents currently in clinical and preclinical studies have the potential to damage the heart (cardiotoxicity). The use of diagnostic imaging, noninvasive stress testing, serum biomarkers, ambulatory blood pressure monitoring, and ambulatory cardiac telemetry (continuous monitoring of a patient's heart from a remote location) can help identify cardiotoxicities and lead to the development of preventative strategies.

DEVELOPING A PROGRAM

Cardio-oncology is a multidisciplinary specialty and requires close collaboration among cardiologists, oncologists, primary care physicians, radiation oncologists, surgeons, and a variety of other specialists involved in the care of cancer patients. An increasing number of national and international programs have developed within the last several years to address this growing clinical need.

In addition to close collaborations with our colleagues across many disciplines, we have implemented several clinical initiatives which have been successful. We created a dedicated cardio-oncology clinic geographically localized within the cancer center. The close proximity with our colleagues in oncology has fostered a greater spirit of collaboration, and embedding our program within the cancer center also exemplified our patient-centered approach. The result of this initiative has been improved patient access and a significant reduction in the time to get an appointment. Timely consultations are critical for many patients, especially when decisions regarding chemotherapy are needed or in cases where cardiotoxicity is a concern.

A second clinical initiative we have successfully implemented is the use of a limited echocardiogram protocol for patients who require routine surveillance of LV ejection fraction while on chemotherapy or after completing chemotherapy. Compared with a comprehensive echocardiogram, this shorter and more focused protocol has improved efficiency in the echo lab and improved patient satisfaction at a reduced cost.

RESEARCH FOCUS

Our group has long been interested in the role of advanced cardiac imaging techniques, including strain imaging by echocardiography, cardiac MRI, and biomarkers in the detection of LV dysfunction in patients receiving chemotherapy.[12-14] Members of our group are also pursuing studies on the molecular mechanisms of anthracycline cardiotoxicity using a novel high-throughput zebrafish model.[15] Collectively, this work could yield better approaches to diagnosis and mitigate the risk of cardiotoxicity.

THE FUTURE

Ongoing clinical trials will address gaps in our knowledge base, with the goal of improving the cardiovascular health outcomes of patients with cancer. Dedicated training experiences in cardio-oncology and educational sessions at national and international meetings (ie, American Heart Association, American College of Cardiology, American Society of Clinical Oncology, European Society of Cardiology, and International CardiOncology Society) will lead to a greater adoption of best practices. Finally, comparative effectiveness studies will guide healthcare policy and influence implementation of clinical cardio-oncology protocols. **EBO**

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PATIENT PERSPECTIVE

Radiation Therapy and Cardiotoxicity: A Cancer Survivor's Story

(CONTINUED FROM COVER)

your radiation and chemotherapy—do it **now**." So I cleared my throat and told them I should probably be seen much sooner than that. I haltingly explained that I had received radiation to the chest and chemotherapy that had included doxorubicin (Adriamycin, a chemotherapy drug that can cause heart muscle damage) about 16 years before, and I was worried that my symptoms could be due to cardiotoxicity from my previous cancer treatment. When I hung up the phone a few moments later, I did so with an appointment scheduled for that day.

The memory that spoke to me so clearly was a brief discussion I'd had many years before with my new radiologist shortly after I had been diagnosed with stage III Hodgkin's lymphoma. I was just 22 years old at the time, trying to cope with my new reality as a young adult with a serious cancer—by taking every moment and making every decision while in the midst of what I now see as a self-protective daze. My oncologist had referred me to the radiologist, explaining that because I had several unfavorable prognostic factors, we needed to consider treatment that included not solely chemotherapy and not solely radiation, but both. The fact was that I had extremely "bulky" disease—meaning that the lymphoma was greater than or equal to 10 centimeters or greater than 33% of my chest diameter on chest x-ray.[1] In addition to having stage III disease, I had also experienced "B symptoms," including severe night sweats and weight loss—the presence of which serve as a marker for more advanced disease with systemic rather than solely localized involvement. So on that long-ago afternoon, my new radiologist was explaining his recommendation for extended-field radiation to the mantle field and periaortal region, and he was reviewing with me the lengthy list of potential adverse effects associated with such treatment. His words describing these possibilities seemed to be flying around me, with none landing, until 2 words managed to break through my daze and push all the others aside. I asked, "Did you just say 'heart damage?'" He had.

Compared with our current understanding, less was known at the time about cardiotoxicity due to radiation. Yet my radiologist did emphasize that, yes, it was possible for patients to manifest what he simply called cardiac damage many years following their radiation treatment. What wasn't known then was that the higher the dose of the radiation, the higher was the risk of developing radiation-induced heart disease.[2] Because my lymphoma was so bulky, the biggest fear was the very real chance of relapse—which, should it occur, would leave me with far fewer and less effective treatment options. At that time (the 1980s), in such cases, 6 weeks of high-dose and extended-field radiation was typical following chemotherapy to reduce the risk of relapse as much as possible. Fortunately, in recent years, there have been ongoing efforts to reduce the extent of radiation treatment for both field size and dose without compromising benefit. In addition, technologic advances have enabled more accurate targeted radiation delivery, which minimizes exposure to the heart and other surrounding normal tissue,[3] though it is not yet clear whether these techniques have lowered the risk of developing late radiation-induced complications overall or served to delay the time to onset of such complications. Therefore, lengthier follow-up is needed to determine the prevalence and pattern of radiation-induced complications with current techniques.[4,5]

But at that time, all this was far off in the future, and there was little choice other than to go ahead with the radiation treatment as prescribed. So I went into "repression mode," figuratively cupping my hands around the 2 words, throwing them back into the swarm that was flying around me, and gratefully returning to my self-protective haze.

I so successfully buried those words that I never thought of them again—until they miraculously roared back into my consciousness at the very moment I needed them. Because from the moment that I called my PCP's office and pushed for an earlier appointment, I realized that it was crucial for me to advocate for myself—and that I needed others to do so as well on my behalf—to survive this.

SELF-ADVOCACY TO ENSURE TREATMENT

During my visit to the PCP's office, the advanced practice registered nurse (APRN) who was examining me began by giving me an electrocardiogram (EKG). I was surprised to learn that my

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DEBRA MADDEN

Ms Madden became an active cancer research advocate following her second cancer diagnosis at the age of 42 years. Nearly 20 years earlier, she had been diagnosed with Hodgkin's lymphoma and subsequently developed late treatment effects, including cardiotoxicity and breast cancer. Debra is currently a member of the ECOG/ACRIN Cancer Research Group and of the Patient-Centered Outcomes Research Institute's Advisory Panel on the Assessment of Prevention, Diagnosis, and Treatment Options. She also serves on multiple grant review panels, including the Congressionally Directed Medical Research Program's Breast Cancer Research Program.

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EKG results were normal. But I was not relieved. I knew that a "normal" EKG does not necessarily mean that you do not have heart problems, and I was worried the EKG results would keep my healthcare providers from further pursuing my symptoms. So I carefully outlined my history to the APRN, explaining that although I was only in my 30s, I had concerns that my symptoms could be due to cardiotoxicity secondary to my radiation, the doxorubicin I'd received during my chemotherapy, or both. She agreed that heart disease was very rare in women my age and that my cancer treatment needed to be taken into account. She thanked me for being candid and for providing specific details about my medical history and explained that she wanted to make a phone call to have me seen by a cardiologist right away.

Years later, my APRN told me about what occurred during that phone call. She explained that when she finally got a cardiologist on the phone, he listened to everything she had to say about my case and responded, "Why are you calling me about this patient? She's far too young for her symptoms to be caused by coronary artery disease." She then again went over my case from the beginning, stressing my history of high-dose radiation to the chest area in my early 20s, my specific chemotherapy regimen, and the nature of my symptoms, including severe chest pain and dyspnea at rest. He listened as she advocated for me, minutes after I'd advocated for myself.

So yes, my EKG was normal—but the test results from my new cardiologist confirmed my fears: severe radiation-induced coronary artery fibrosis (scarring), stenosis (narrowing), and 90% blockage. The worsening chest pain I'd been experiencing was due to reduced flow of oxygenated blood to my heart, caused by progressive narrowing of one of my coronary arteries.

A SECOND OPINION...OR SEVERAL

Due to the complexity of my case, my cardiologist quickly brought in a colleague, an interventional cardiologist. He explained that because of the specific location of my blockage, there was concern over whether the better course of action would be a coronary artery bypass graft (CABG) or an angioplasty.

When my husband and I met with this second cardiologist, his demeanor was extremely grave as he explained the severity of my blockage and the risks associated with both procedures. At one point, when he was showing us images of my heart and the coronary arteries, I asked him point-blank, "Should I be getting my affairs in order?" He simply said, "Yes." I was blindsided by his response. Although I'd asked the question, I expected reassurance. When I heard instead his devastating response, time instantly divided—into before the "yes" and after—and that's when the tears came. They didn't stop during our long drive home, and they came harder when I thought about having to share this bad news with my parents. I simply couldn't bear it, so I asked my poor husband to call them for me. He did so as soon as we arrived home, as I listened, still in tears.

My cardiologists, in turn, brought my case for review before a large team of cardiologists—including invasive, interventional, and surgical cardiologists—due to the difficult location of the blockage and the distinct risk of having another coronary artery collapse during an angioplasty. After conferencing, their overall recommendation was to conduct an angioplasty with placement of a drug-eluting stent, which had just been approved by the FDA the month before. But they also stressed the need to have a team of cardiac surgeons on hand to perform a CABG should a second artery indeed collapse, leading to a risk of myocardial infarction (MI) during the procedure. And whether to go with angioplasty or directly to a CABG was 100% my choice. It was one of the most agonizing decisions I had ever made. Ultimately, I chose the angioplasty. And

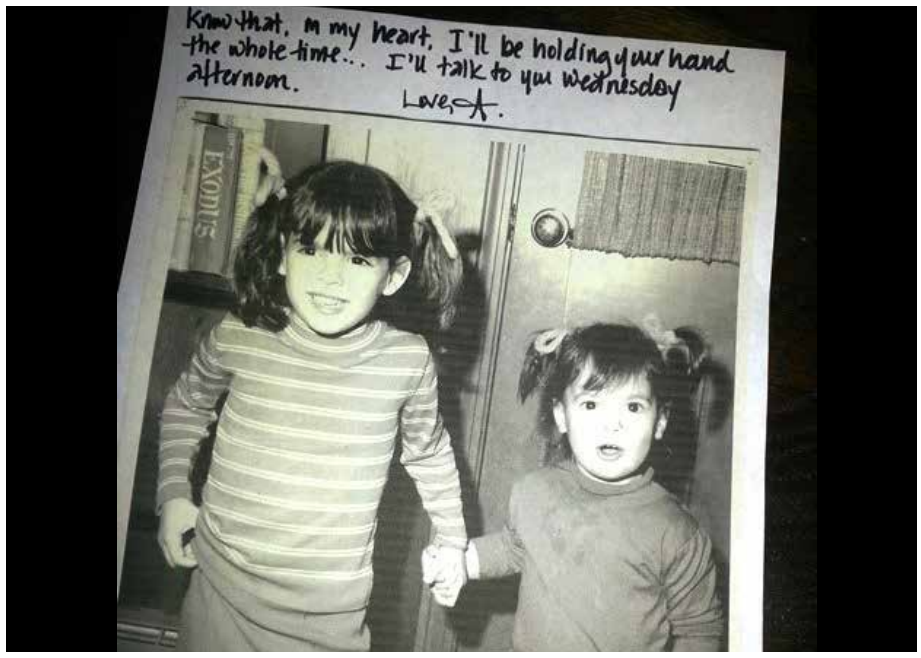
When my husband and I met with this second cardiologist, his demeanor was extremely grave as he explained the severity of my blockage and the risks associated with both procedures. At one point, when he was showing us images of my heart and the coronary arteries, I asked him point-blank, "Should I be getting my affairs in order?" He simply said, "Yes."

during the operation, my cardiologists' and my own fears came true: a second coronary artery did in fact collapse during the procedure. But fortunately, a CABG was not the option chosen by my cardiologists. I later learned that because the drug-eluting stent they used during my first angioplasty was so newly FDA-approved, their quantities were extremely limited—and the cardiologists therefore needed to lobby strongly for approval to place a second stent. To my good fortune, their efforts were successful: the team was able to immediately do a second angioplasty and place the second stent. At the end of my successful procedure, both of my cardiologists were visibly relieved. I was profoundly grateful to them then, and remain grateful today and every day, for they both became advocates on my behalf as well, helping me to survive the most frightening moments of my life.

I knew then and know now just how fortunate I was that my radiation-induced coronary blockage was diagnosed before my symptoms worsened even further. Overall, for Hodgkin's patients who have been treated with radiation, cardiovascular disease is the most common cause of death after malignant disease, most frequently occurring decades after their treatment. These patients have an increased risk for coronary artery disease, congestive heart failure, valvular heart disease, and sudden cardiac death, with the risk particularly high in those who were treated before the age of 40 years. The relative risk of death from a fatal MI in patients who received mediastinal radiation therapy is increased from between 1.5 and 3.0 times that of patients who have not received radiation.[5]

CONTINUING NEED FOR ADVOCACY

Years following my angioplasties, during a routine follow-up visit, my cardiologist shared with me that I was the first patient he'd diagnosed and treated for radiation-induced coronary artery disease due to cancer treatment. And I know that his advocacy on behalf of patients has extended far beyond my original case. For example, just months after my procedure, he told me he had emergently treated a young man who had also had Hodgkin's lymphoma and developed cardiac symptoms as a late effect of his cancer treatment. In addition, he has given grand rounds—an important teaching tool in medical education and patient care for doctors, residents, and medical students—on recognizing and treating radiation-induced cardiotoxicity in young adult cancer survivors. And now I'm turning to you, the reader, in the hope that you will join in advocacy efforts as well. It remains true



Shortly before my procedure, my younger sister sent me the above message with this childhood photo of the 2 of us—with words I'll always treasure.

that few PCPs, generalists, and patients are sufficiently aware of the late effects that may develop often decades after cancer treatment, no matter the patient's age. Yet with so many cancer patients now surviving their disease and ultimately returning to their PCPs for their medical care, there is an urgent need for these physicians and their patients to develop a more specific understanding of long-term, late, and secondary adverse effects of particular cancer treatments, including cardiotoxicity and second cancers. I'm gratified that *The American Journal of Managed Care* has taken a critical step toward achieving this by devoting this edition of *Evidence-Based Oncology* to the growing subspecialty of cardio-oncology. Please consider "paying it forward" by sharing this important issue with loved ones and friends affected by cancer and urging them to do likewise with their PCPs. **EBO**

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HEALTHCARE POLICY

Advancing Patient Care in Cardio-Oncology: The ACC.15 Cardio-Oncology Intensive

(CONTINUED FROM COVER)

broader interdisciplinary dialogue and bringing multiple stakeholders to the stage. In collaboration with the organizing committee of the 64th Annual Scientific Sessions (ACC.15), chaired by Athena Poppas, MD, and Jeffrey T. Kuvin, MD, Working Group members designed a Cardio-Oncology Intensive—a half-day program focused on highly relevant clinical questions in the CV care of patients with cancer and cancer survivors. The aim of the Intensive, which took place March 16, 2015, in San Diego, was to initiate a dynamic conversation on different aspects of care, and utilize novel presentation formats to facilitate audience participation and learning. Importantly, all debates and panel discussions included members of both cardiology health teams and oncology health teams, thereby allowing the audience to glean perspectives on patient care from both sides of the aisle.

The Intensive opened with an overview that consisted of a cardiologist's perspective of cardio-oncology, followed by an oncologist's perspective. The cardiologist, Pamela Douglas, MD, MACC, FASE, of Duke University, called for guidelines and a multidisciplinary approach to the care of these patients, highlighting overlap and common risk factors such as smoking, obesity, poor nutrition, and inflammation shared by cancer and heart disease patients. Subsequently, oncologist Susan Dent, MD, of the Ottawa Hospital Cancer Centre and the University of Ottawa took the stage and underscored the rising trend in mortality due to heart disease in breast cancer survivors, calling for collaboration between both groups as an important aid in avoiding heart damage when possible.

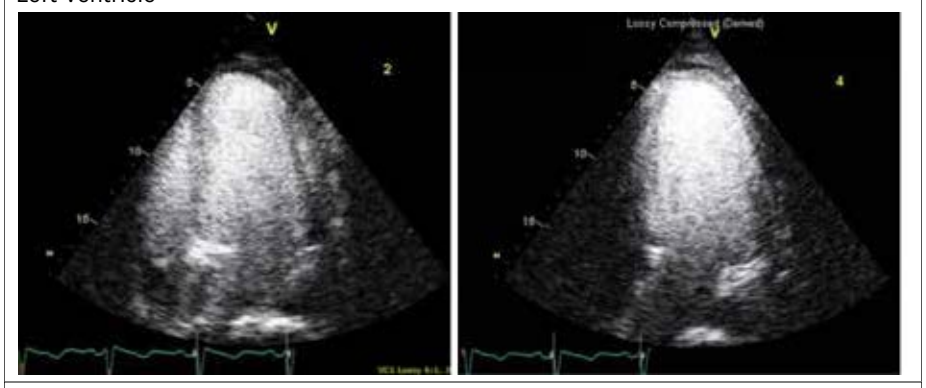
CASE DISCUSSION

The Intensive session included 4 case presentations that covered areas of CV risk prediction and cardioprotection strategies in patients undergoing cancer therapies, delivery of comprehensive care in cancer survivorship, and management of patients treated with vascular endothelial growth factor (VEGF) signaling pathway inhibitors. Here we highlight a case that presented current challenges in CV risk stratification and brought to the table experts in CV imaging, biomarkers for risk stratification, oncology treatment, and CV risk modeling.

Case Presentation

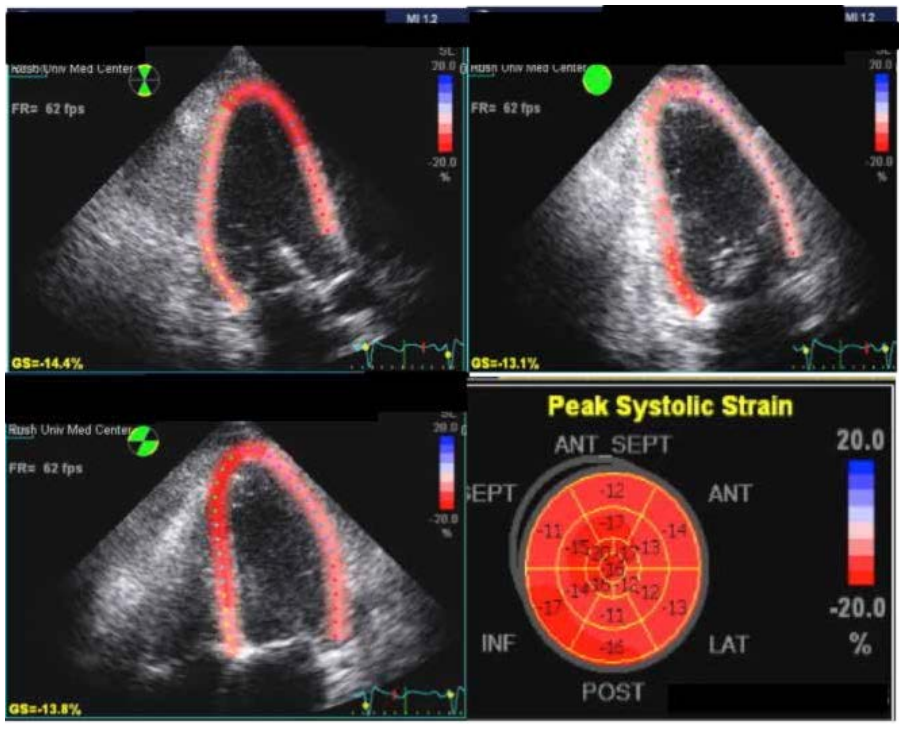
A 68-year-old African American woman with new diagnosis of stage III diffuse large B-cell lymphoma was referred for an evaluation of CV risk prior to initiation of planned chemotherapy treatment. Her medical history included left-sided infiltrating ductal carcinoma of the breast (stage IIIB, hormone receptor–negative and HER2 receptor-negative) at age 31 years, for which she received left modified radical mastectomy, post mastectomy chest wall irradiation, and doxorubicin, cyclophosphamide, and paclitaxel chemotherapy. Her history was also significant for hypertension controlled with medications, obesity, 7-year history of type 2 diabetes mellitus, and shoulder arthritis. Her medications included metformin, chlorthalidone, simvastatin, aspirin, ibuprofen, and insulin with meals. The physical exam revealed elevated blood pressure but normal CV exam without elevated jugular venous pressure. She denied angina-like symptoms. The electrocardiogram (ECG) showed normal sinus rhythm, and troponin I and brain natriuretic peptide (BNP) were within normal ranges. The patient underwent a stress echocardiogram (ECHO) with myocardial strain assessment that demonstrated mildly reduced systolic function at rest with overall LVEF of 50% (see **FIGURE 1**) and abnormal global longitudinal strain value of –14.5% (see **FIGURE 2**). There was preserved contractility during stress, without regional wall motion abnormalities. The patient's medical therapy was optimized by introduction of an ACE inhibitor and a beta-blocker: lisinopril and carvedilol, respectively. Blood pressure lowering was pursued to a goal of less than 130/80 mm Hg. Chlorthalidone was stopped to allow titration of the ACE inhibitor and beta-blocker. Simvastatin was switched to pravastatin while on chemotherapy, and ibuprofen was discontinued. Therapeutic lifestyle changes were recommended, including increasing walking and other

FIGURE 1. ECHO Contrast Images Showing Apical 4- and 2-Chamber Views of the Left Ventricle



Stress echo with left ventricular ejection fraction assessment with contrast was performed prior to myocardial stain imaging.

FIGURE 2. Left Ventricular Myocardial Strain Speckle Tracking Images



Apical 3-chamber, 2-chamber, and 4-chamber projection of left ventricular myocardial strain imaging by echocardiography, with bull's-eye showing average global longitudinal strain (GS) of –14.5%.

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exercise, improved diet (referral to a dietician was provided), as well as stress reduction. She was treated with 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone regimen (R-CHOP) with dexrazoxane infusions. She had a good outcome and continues to be followed.

PANEL DISCUSSION

The conversation began with a discussion on elevated CV risk in light of planned therapy with R-CHOP. With a history of treatment for breast cancer that included 240 mg/m^2 of doxorubicin in the past, planned R-CHOP treatment was raising the cumulative doxorubicin dose to a high value of 540 mg/m^2. The panel recognized the lack of randomized data for cardiac prevention in this patient and necessary extrapolation from CV data derived in different cohorts.

Use of Strain Imaging

Thomas Marwick, MD, PhD, MPH, cardiologist at the Menzies Research Institute, Tasmania, and formally of the Cleveland Clinic, reviewed the evidence for incremental value of ECHO strain imaging in predicting cardiotoxicity in patients undergoing cancer treatment.[2] Normal ranges and important technical considerations were discussed, including imaging and post processing, as well as variations in strain data interpretation related to regional heterogeneity, load-independence, and different vendors.[3] The understanding of these concepts will be critical for wider clinical implementation of strain, including in the care of patients with different malignancies, as well as in the design of clinical studies investigating the utility of strain in guiding cardioprotective treatment.

Use of Biomarkers

Daniel Lenihan, MD, cardiologist at the Vanderbilt Heart and Vascular Institute in Nashville, discussed the role of BNP as a biomarker and predictor of cardiotoxicity that showed promise in smaller trials.[4] While we await the completion of the ongoing multicenter PREDICT study, we'd like to direct the readers to its positive preliminary findings presented at recent national meetings.[5]

Use of Cardiac MR

W. Gregory Hundley, MD, FACC, FAHA, cardiologist at the Wake Forest Baptist Health, highlighted the advantages of using cardiac magnetic resonance, including high accuracy and reproducibility of ventricular volume measurements of a particular value in patients undergoing serial imaging. He also described novel data on extracellular volume measurement using T1 mapping as a promising new marker of cardiotoxicity.[6,7]

Oncology Treatment Considerations

Erica Mayer, MD, MPH, oncologist at Dana-Farber Cancer Institute, commented on the success of triple-negative breast cancer treatment in this patient 30 years prior to her presentation with the second malignancy, and highlighted the national trend of decreasing the use of anthracyclines in the treatment of patients with breast cancer.[8] The consideration of dexrazoxane was discussed, as was the need for prospective evaluation of this and other cardioprotective agents in conjunction with specific oncology regimens.

Models to Predict CV Risk

CV risk prediction models in patients with cancer are scarce and Jersey Chen, MD, MPH, cardiologist and clinical development physician at AstraZeneca, presented recently published risk score data for cardiomyopathy and heart failure in patients with breast cancer who received trastuzumab. This model utilized the Surveillance, Epidemiology and End Results (SEER)-Medicare database and identified 7 risk factors including age, adjuvant chemotherapy, coronary artery disease, atrial fibrillation, diabetes mellitus, hypertension. and renal failure.[9] The model was contrasted with another cardiac risk score derived among clinical trial participants that identified age and baseline left ventricular ejection fraction as the only important contributors to risk in patients receiving trastuzumab therapy.[10] The need for further validation of these models in clinical practice was highlighted, as well as the need for development of CV risk prediction in patients with other malignancies.

Rapid developments in oncology and cardiology have created a durable need for platforms that allow knowledge exchange and interdisciplinary education.

The Intensive continued with case presentations and a discussion of how to deliver comprehensive care to patients, highlighted by expert commentaries on cancer survivorship and exercise. The talk on the cardiotoxic effects of the VEGF signaling pathway inhibitors focused on the need for and approaches to ischemia evaluation. The debate on the cardiotoxicity related to radiation therapy presented novel modalities, posing the question of whether radiation effects continue to be an ongoing concern. Each of these clinical areas (and more which could not be addressed within the allotted time) represents a unique need and opportunity for growth and collaboration among oncologists, cardiologists, and other medical staff, as well as among various CV subspecialties involved in the evaluation of cancer patients presenting with CV disease and/or risk factors.

Rapid developments in oncology and cardiology have created a durable need for platforms that allow knowledge exchange and interdisciplinary education. The ACC.15 Cardio-Oncology Intensive successfully joins the effort to advance scientific dialogue and bridge gaps in clinical practice through education and collaboration. As we plan the next Intensive, it is important to note broad areas of partnership that will need to be developed in order to advance CV care of patients with cancer and cancer survivors. They include but are not limited to:

- collaborations in clinical guidelines and documents development;
- education and clinical training;
- database and registry building; and
- basic, clinical, translational, and epidemiology research.[1]

The ACC's newly formed Cardio-Oncology Section is a demonstration of the Society's commitment to advance patient care and to play an active role in the future growth of this field.

The authors would like to thank the faculty and all participants of the ACC.15 Cardio-Oncology Intensive for their contributions. **EBO**

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