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PCOC15 PATIENT-CENTERED ONCOLOGY CARE®

EXCLUSIVE COVERAGE!

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imbruvica®
(ibrutinib) 140mg capsules

DISCOVERING HOW FAR THERAPY CAN GO

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

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

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

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

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

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.

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).

ADVERSE REACTIONS

The most common adverse reactions (≥25%) in patients with B-cell malignancies (MCL, CLL, WM) were thrombocytopenia* (57%, 52%, 43%), neutropenia* (47%, 51%, 44%), diarrhea (51%, 48%, 37%), anemia* (41%, 36%, 13%), fatigue (41%, 28%, 21%), musculoskeletal pain (37%, 28%†, NA‡), bruising (30%, 12%†, 16%†), nausea (31%, 26%, 21%), upper respiratory tract infection (34%, 16%, 19%), and rash (25%, 24%†, 22%†).

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

†Includes multiple ADR terms.

‡Not applicable; no associated ADRs.

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

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

Approximately 5% (CLL), 9% (MCL), and 6% (WM) of patients discontinued due to adverse events. Most frequent adverse events leading to discontinuation were infections, subdural hematomas, and diarrhea in CLL patients and subdural hematoma (1.8%) in MCL patients.

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 pages.

To learn more, visit
www.IMBRUVICA.com

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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.

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Dennis P. Scanlon, PhD, served as moderator for the first day of Patient-Centered Cancer Care 2015.

Setting the Agenda for Stakeholders

For the 4th year, *The American Journal of Managed Care* presented Patient-Centered Oncology Care in Baltimore, Maryland. As usual, the meeting on November 19-20, 2015, fulfilled its mission of bringing together stakeholders from across cancer care for a one-of-a-kind experience: to hear from others they would not meet at their own professional meeting or during the work day, but whose lives and experiences are central to their own. We know we've succeeded when first-time attendees say they'll see us next year, because they've never encountered a meeting quite like ours. As always, Patient-Centered Oncology Care proved to be timely. It was clear during our planning that the FDA's interest in regulating diagnostic tests would be an emerging topic, and our panel with former officials from FDA and CMS ended up discussing a report just a few weeks old. Our keynote speaker, Dr Julie Vose, the current president of the American Society of Clinical Oncology, addressed the impact of brand-new legislation that will affect the way every oncologist gets paid. Multiple speakers took on the topic of high drug costs, just as the topic was gaining traction among presidential candidates. We heard from patients, too. Jack Whelan shared his experience as an educated patient and advocate, and we heard from patients indirectly through Duke University's, Dr Yousuf Zafar, whose work on how the cost of therapy affects outcomes has given us the term "financial toxicity."

MIKE HENNESSY, SR

Years before the cost of cancer therapy was on Congress' agenda, Patient-Centered Oncology Care brought stakeholders together to foster this important conversation. At *The American Journal of Managed Care,* we are committed to promoting dialogue on value in cancer care, and we encourage you to join us. It's not too soon to put Patient-Centered Oncology Care 2016 on your calendar—plan to join us November 17-18, 2016.For a current update on other clinical meetings and news, please visit us at www.ajmc.com.

Sincerely,

Mike Hennessy, Sr
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.

GRANIX® (TBO-FILGRASTIM) Injection

New J Code & Billing Unit
Effective January 1, 2016
J 1447 Injection, tbo-filgrastim, 1 microgram

Trusted to take a bite out of G-CSF acquisition costs

Based on wholesale acquisition cost (WAC) of short-acting G-CSF products as of 11-2015. Transactional prices may vary; contact your supplier for actual prices.

GRANIX® has gained 38% share of the US short-acting G-CSF hospital market in its first 22 months[1]

- A 71% reduction in duration of severe neutropenia vs placebo (1.1 days vs 3.8 days, $p<0.0001$)[2]
  - Efficacy was evaluated in a multinational, multicenter, randomized, controlled, Phase III study of chemotherapy-naïve patients with high-risk breast cancer receiving doxorubicin (60 mg/m^2 IV bolus)/docetaxel (75 mg/m^2)[2]
- The safety of GRANIX was established in 3 Phase III trials, with 680 patients receiving chemotherapy for either breast cancer, lung cancer, or non-Hodgkin lymphoma (NHL)[2]
- Offering a presentation for self-administration

- GRANIX is a leukocyte growth factor indicated for reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

Important Safety Information

- **Splenic rupture:** Splenic rupture, including fatal cases, can occur following the administration of human granulocyte colony-stimulating factors (hG-CSFs). Discontinue GRANIX and evaluate for an enlarged spleen or splenic rupture in patients who report upper abdominal or shoulder pain after receiving GRANIX.
- **Acute respiratory distress syndrome (ARDS):** ARDS can occur in patients receiving hG-CSFs. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.
- **Allergic reactions:** Serious allergic reactions, including anaphylaxis, can occur in patients receiving hG-CSFs. Reactions can occur on initial exposure. Permanently discontinue GRANIX in patients with serious allergic reactions. Do not administer GRANIX to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.
- **Use in patients with sickle cell disease:** Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disease receiving hG-CSFs. Consider the potential risks and benefits prior to the administration of GRANIX in patients with sickle cell disease. Discontinue GRANIX in patients undergoing a sickle cell crisis.
- **Capillary leak syndrome (CLS):** CLS can occur in patients receiving hG-CSFs and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of CLS should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.
- **Potential for tumor growth stimulatory effects on malignant cells:** The granulocyte colony-stimulating factor (G-CSF) receptor, through which GRANIX acts, has been found on tumor cell lines. The possibility that GRANIX acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which GRANIX is not approved, cannot be excluded.
- **Most common treatment-emergent adverse reaction:** The most common treatment-emergent adverse reaction that occurred in patients treated with GRANIX at the recommended dose with an incidence of at least 1% or greater and two times more frequent than in the placebo group was bone pain.

Please see brief summary of Full Prescribing Information on adjacent page.

For more information, visit GRANIXhcp.com.

References: 1. This information is an estimate derived from the use of information under license from the following IMS Health Information Service: IMS National Sales Perspective, GRANIX micrograms by non-federal hospital channel September 2015. IMS expressly reserves all rights, including rights of copying, distribution, and republication (micrograms calculated as eaches x strength). **2.** GRANIX® (tbo-filgrastim) Injection Prescribing Information. North Wales, PA: Teva Pharmaceuticals; 2014.

TEVA Oncology

GRANIX® (TBO-FILGRASTIM) Injection

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR
GRANIX® (tbo-filgrastim) injection, for subcutaneous use
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GRANIX is indicated to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

Splenic rupture, including fatal cases, can occur following administration of human granulocyte colony-stimulating factors. In patients who report upper abdominal or shoulder pain after receiving GRANIX, discontinue GRANIX and evaluate for an enlarged spleen or splenic rupture.

5.2 Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) can occur in patients receiving human granulocyte colony-stimulating factors. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.

5.3 Allergic Reactions

Serious allergic reactions including anaphylaxis can occur in patients receiving human granulocyte colony-stimulating factors. Reactions can occur on initial exposure. The administration of antihistamines, steroids, bronchodilators, and/or epinephrine may reduce the severity of the reactions. Permanently discontinue GRANIX in patients with serious allergic reactions. Do not administer GRANIX to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.

5.4 Use in Patients with Sickle Cell Disease

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disease receiving human granulocyte colony-stimulating factors. Consider the potential risks and benefits prior to the administration of human granulocyte colony-stimulating factors in patients with sickle cell disease. Discontinue GRANIX in patients undergoing a sickle cell crisis.

5.5 Capillary Leak Syndrome

Capillary leak syndrome (CLS) can occur in patients receiving human granulocyte colony-stimulating factors and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

5.6 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

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

6 ADVERSE REACTIONS

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

- Splenic Rupture [*see Warnings and Precautions (5.1)*]
- Acute Respiratory Distress Syndrome [*see Warnings and Precautions (5.2)*]
- Serious Allergic Reactions [*see Warnings and Precautions (5.3)*]
- Use in Patients with Sickle Cell Disease [*see Warnings and Precautions (5.4)*]
- Capillary Leak Syndrome *[see Warnings and Precautions (5.5)]*
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [*see Warnings and Precautions (5.6)*]

The most common treatment-emergent adverse reaction that occurred at an incidence of at least 1% or greater in patients treated with GRANIX at the recommended dose and was numerically two times more frequent than in the placebo group was bone pain.

6.1 Clinical Trials Experience

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

GRANIX clinical trials safety data are based upon the results of three randomized clinical trials in patients receiving myeloablative chemotherapy for breast cancer (N=348), lung cancer (N=240) and non-Hodgkin's lymphoma (N=92). In the breast cancer study, 99% of patients were female, the median age was 50 years, and 86% of patients were Caucasian. In the lung cancer study, 80% of patients were male, the median age was 58 years, and 95% of patients were Caucasian. In the non-Hodgkin's lymphoma study, 52% of patients were male, the median age was 55 years, and 88% of patients were Caucasian. In all three studies a placebo (Cycle 1 of the breast cancer study only) or a non-US-approved filgrastim product were used as controls. Both GRANIX and the non-US-approved filgrastim product were administered at 5 mcg/kg subcutaneously once daily beginning one day after chemotherapy for at least five days and continued to a maximum of 14 days or until an ANC of ≥10,000 x 10^6/L after nadir was reached.

Bone pain was the most frequent treatment-emergent adverse reaction that occurred in at least 1% or greater in patients treated with GRANIX at the recommended dose and was numerically two times more frequent than in the placebo group. The overall incidence of bone pain in Cycle 1 of treatment was 3.4% (3.4% GRANIX, 1.4% placebo, 7.5% non-US-approved filgrastim product).

Leukocytosis

In clinical studies, leukocytosis (WBC counts > 100,000 x 10^6/L) was observed in less than 1% patients with non-myeloid malignancies receiving GRANIX. No complications attributable to leukocytosis were reported in clinical studies.

Additional Adverse Reactions

Other adverse reactions known to occur following administration of human granulocyte colony-stimulating factors include myalgia, headache, vomiting, Sweet's syndrome (acute febrile neutrophilic dermatosis), cutaneous vasculitis and thrombocytopenia.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving GRANIX has not been adequately determined.

7 DRUG INTERACTIONS

No formal drug interaction studies between GRANIX and other drugs have been performed.

Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of GRANIX in pregnant women. In animal reproduction studies, treatment of pregnant rabbits with tbo-filgrastim resulted in increased spontaneous abortion and fetal malformations at systemic exposures substantially higher than the human exposure. GRANIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

In an embryofetal developmental study, pregnant rabbits were administered subcutaneous doses of tbo-filgrastim during the period of organogenesis at 1, 10 and 100 mcg/kg/day. Increased abortions were evident in rabbits treated with tbo-filgrastim at 100 mcg/kg/day. This dose was maternally toxic as demonstrated by reduced body weight. Other embryofetal findings at this dose level consisted of post-implantation loss, decrease in mean live litter size and fetal weight, and fetal malformations such as malformed hindlimbs and cleft palate. The dose of 100 mcg/kg/day corresponds to a systemic exposure (AUC) of approximately 50-90 times the exposures observed in patients treated with the clinical tbo-filgrastim dose of 5 mcg/kg/day.

8.3 Nursing Mothers

It is not known whether tbo-filgrastim is secreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GRANIX is administered to a nursing woman. Other recombinant G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates.

8.4 Pediatric Use

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

8.5 Geriatric Use

Among 677 cancer patients enrolled in clinical trials of GRANIX, a total of 111 patients were 65 years of age and older. No overall differences in safety or effectiveness were observed between patients age 65 and older and younger patients.

8.6 Renal Impairment

The safety and efficacy of GRANIX have not been studied in patients with moderate or severe renal impairment. No dose adjustment is recommended for patients with mild renal impairment.

8.7 Hepatic Impairment

The safety and efficacy of GRANIX have not been studied in patients with hepatic impairment.

10 OVERDOSAGE

No case of overdose has been reported.

TEVA Oncology

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Sicor Biotech UAB
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North Wales, PA 19454

Product of Israel

GRX-40580 January 2015

This brief summary is based on TBO-004 GRANIX full Prescribing Information.

KEYNOTE SPEAKER

Julie M. Vose, MD, MBA, FASCO
Neumann M. and Mildred E. Harris Professor
Chief, Division of Oncology/Hematology
Department of Internal Medicine
University of Nebraska Medical Center
Omaha, NE

Dr Vose is the Neumann M. and Mildred E. Harris Professor and chief in the Division of Oncology/Hematology at the University of Nebraska Medical Center in Omaha, Nebraska. Dr Vose received her medical degree, completed her residency in internal medicine, served as chief resident, and completed a fellowship in hematology/oncology at the University of Nebraska Medical Center. She completed a sabbatical at Stanford University and received her MBA in health administration through the University of Colorado Business School.

Dr Vose has focused her career on translational research for improvement in the therapy of non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma by developing a focused translational research program evaluating novel therapies such as radiolabeled monoclonal antibodies, idiotype vaccine therapies, pathway-directed agents, and stem-cell transplantation. She has been recognized for her NHL research on the national and international level through research awards and invited lectureships worldwide. In addition, her funding record and publications in NHL therapy and transplantation research have added substantially to the research and knowledge base for the therapy of lymphoma. She is currently 2015-2016 president of the American Society of Clinical Oncology.

MODERATORS

Bruce A. Feinberg, DO
Vice President and Chief Medical Officer
Clinical Pathways
Cardinal Health Specialty Solutions
Dublin, OH

Dr Feinberg is recognized for his expertise in oncology and the business of specialty health care. He serves as vice president and chief medical officer for the Clinical Pathways business of Cardinal Health Specialty Solutions. Clinical Pathways aims to control costs, improve the quality of care, and increase predictability—which are critical goals for payers and providers who drive the pathways process.

Prior to joining the Cardinal Health team, Dr Feinberg was instrumental in establishing Georgia Cancer Specialists (GCS), the largest and first integrated oncologic specialty practice in the Southeast. As CEO and president of GCS, he expanded community access to oncology care by bringing the latest cancer treatments, technologies, and clinical trials closer to the patient. In 2012, Specialty Solutions launched PathWare Decision Transaction Solutions, a software technology Dr Feinberg was instrumental in designing, to improve the workflow process for payers and physicians. Dr Feinberg is the author of the bestselling *Breast Cancer Answers* and its follow-up book, *Colon Cancer Answers*.

An early adopter of information technology, he incorporated electronic medical records (EMRs) at GCS in 1999 and subsequently developed OASIS, a proprietary EMR software application that incorporates artificial intelligence logic into common EMR functions. Dr Feinberg is the innovator behind Chemoorders.com, a free, online disease-management system for health care providers. Launched in June 2007, ChemoOrders.com now has in excess of more than 10,000 visitors and thousands of regular users worldwide.

Dennis P. Scanlon, PhD
Professor of Health Policy and Administration
Director of the Center for Health Care
and Policy Research
Penn State University, University Park, PA

Dr Scanlon is professor of health policy and administration in the College of Health and Human Development and director of the Center for Health Care and Policy Research, both at The Pennsylvania State University. His research focuses on understanding the roles of measurement, incentives, quality improvement, and individual and organizational behavioral changes in improving important health care outcomes, including clinical quality, patient experience, and economic efficiency. Dr Scanlon serves on the editorial board of several journals, including *Health Services Research* and *Medical Care Research and Review*. He was recently appointed associate editor of *The American Journal of Managed Care*.

He was the 2014 recipient of the Evan G. and Helen G. Pattishall Outstanding Research Achievement Award, given by the College of Health and Human Development at Penn State. This award honors a faculty member's outstanding research contributions occurring or culminating within the past several years. In 2005, he was also the recipient of the Fran and Holly Soistman Faculty Development Award, which honors a faculty member's engagement in significant, innovative research related to the design development, delivery, administration, or evaluation of health care services, also given by the College of Health and Human Development. In 2002, he received the John D. Thompson Prize for Young Investigators, given annually by the Association of University Programs in Health Administration to an outstanding young investigator in the field of health services research, and the Robert Wood Johnson Foundation's (RWJF) Investigator in Health Policy Research Award.

Dr Scanlon has served on several national, local, and international advisory panels for organizations such as the Agency for Healthcare Research & Quality, the National Quality Forum, the Commonwealth of Pennsylvania, and the European Commission. He is currently serving as the principal investigator for the evaluation of RWJF's Aligning Forces for Quality program and has published more than 100 articles, book chapters, and reports. Dr. Scanlon completed a bachelor's degree at Villanova University, a master of economics from the University of Pittsburgh, and a doctorate in health services organization and policy at the University of Michigan.

FACULTY

Joseph Alvarnas, MD
Director of Value-Based Analytics
City of Hope
Duarte, CA

Dr Alvarnas attended medical school at the University of California, San Francisco. He completed internal medicine training and fellowships in hematology and hematopoietic cell transplantation at Stanford University Medical Center. He worked at the City of Hope Banner Transplant Program, which he helped found. He subsequently worked as director of the Hematopoietic Stem Cell Processing Laboratory and chair of the Quality Committee for the transplant program. He is currently an associate clinical professor in the Department of Hematology/Hematopoietic Cell Transplantation at the City of Hope, where he also serves as the director of value-based analytics for the institution. He is national co-chair for 2 Bone Marrow Transplant Clinical Trials Network clinical trials studying stem-cell transplantation in HIV-infected patients. Dr Alvarnas serves on the American Society of Hematology Committee on Practice and as an ASH liaison to the Committee on Quality.

Peter B. Bach, MD, MAPP

Director, Center for Health Policy and Outcomes
Memorial Sloan Kettering Cancer Center
New York, NY

Dr Bach's main research interests cover healthcare policy, particularly as it relates to Medicare, racial disparities, in cancer care quality, and lung cancer epidemiology. A former senior adviser to the administrator of CMS, he serves on several national committees, including the Institute of Medicine's National Cancer Policy Forum and the Committee on Performance Measurement of the National Committee on Quality Assurance. In 2015, he released MSKCC's DrugAbacus, the first interactive tool to set a cancer drug's price based on its value compared with the price set by its manufacturer. Dr Bach received his bachelor's degree from Harvard and his medical degree from the University of Minnesota. He received a Masters of Arts in Public Policy from the University of Chicago.

John Fox, MD, MHA

Senior Medical Director
Priority Health
Grand Rapids, MI

Dr Fox is senior medical director and vice president of Medical Affairs for Priority Health, a provider-sponsored health plan with 640,000 members headquartered in Grand Rapids, Michigan. Dr Fox is responsible for technology assessment, total cost of care management, and innovations. These innovations include pay-for-value contracting, integrated specialty pharmacy management, consumer transparency, surgical optimization initiatives, and medical home programs.

Prior to joining Priority Health, Dr Fox was the chief medical officer at Physicians Plus Insurance in Madison, Wisconsin. He has also worked for the Indian Health Service and with the Epidemic Intelligence Service in the Centers for Disease Control and Prevention (CDC).

Dr Fox's current interests include specialty pharmacy management, the use of cost-effectiveness and number-needed-to-treat analyses in coverage determinations, and the effect of behavioral economics on health outcomes.

Dr. Fox received his medical degree from Johns Hopkins University School of Medicine and a master's degree in health administration from the University of Wisconsin. He completed a pediatric internship and residency at the Johns Hopkins Hospital and a fellowship in epidemiology at the CDC.

Scott Gottlieb, MD

Resident Fellow
American Enterprise Institute
Washington, DC

Dr Gottlieb is a practicing physician and resident fellow at the American Enterprise Institute. From 2003-2004, Dr Gottlieb served as a senior advisor to the FDA Commissioner and as the FDA's director of Medical Policy Development. From there, between 2005 and 2007, he served as FDA deputy commissioner for Medical and Scientific Affairs. In between, he left the FDA in the spring of 2004 to work on implementation of the new Medicare Drug Benefit as a senior adviser to the administrator of the Centers for Medicare & Medicaid Services. Dr Gottlieb is an editorial board member of the journal *Value Based Cancer Care,* the Food and Drug Law Institute's Policy Forum, and is a member of the board of advisers of Cancer Commons. He also writes a regular column for the *Wall Street Journal*. Dr Gottlieb is a member of the policy boards to the Society of Hospitalist Medicine and the Leukemia and Lymphoma Society, and serves as a consultant and director to public and private life science and health care services companies. He also serves as an advisor to investors in life sciences. Dr Gottlieb is a clinical assistant professor at the New York University School of Medicine. He completed a residency in internal medicine at the Mount Sinai Hospital in New York and is a graduate of the Mount Sinai School of Medicine and of Wesleyan University, in Middletown, Connecticut, where he studied economics.

Robert Green, MD

Vice President, Clinical Strategy & Senior Medical Director
Flatiron Health
New York, NY

Dr Green is a medical oncologist, vice president of clinical strategy, and senior medical director at Flatiron Health, where he oversees clinical development of OncoEMR, the leading electronic medical record for medical oncology, and OncoAnalytics, a first-of-its-kind advanced analytics tool that unlocks meaningful data from multiple systems across various vendors. Dr Green also oversees clinical affairs and works with Flatiron's value-based care team to help practices participate in alternative payment models.

Prior to joining Flatiron Health, Dr Green was a managing partner at Palm Beach Cancer Institute and helped lead its merger with Florida Cancer Specialists (FCS) in 2013. He served 2 years as chief medical officer of Cancer Clinics of Excellence. He currently serves on the board of the Community Oncology Alliance and is a former executive board member at FCS.

Dr Green received his undergraduate and medical degrees at Duke University and a master of science in clinical epidemiology and biostatistics degree at the University of Pennsylvania. He also completed his internship, residency, and fellowship in medical oncology at the University of Pennsylvania. Dr Green continues to see patients in West Palm Beach Florida at FCS on a part-time basis.

Daniel J. Klein, MHS

President and CEO
The Patient Access Network Foundation

Mr Klein brings over 30 years of executive experience to the Patient Access Network (PAN) Foundation. Mr Klein came to the PAN Foundation from the Cystic Fibrosis (CF) Foundation, where he was senior vice president for patient access programs and, prior to that, senior vice president for the CF Services specialty pharmacy.

His leadership at the CF Foundation was exemplified by the CF Services pharmacy that he helped organize and implement to provide financial assistance and case-management services for underinsured patients with CF. While running the CF Services pharmacy, he also developed a pharmaceutical call center business unit to support the launch of new specialty medications for patients with CF.

Mr. Klein has had numerous leadership roles in the health and information technology sectors, including as chairman and CEO of Panurgy Corporation, a leading mid-market information technology services company, as well as a consultant on health planning for the World Health Organization and health promotion the US Department of Health and Human Services.

Michael A. Kolodziej, MD

National Medical Director
Oncology Strategy Office
Aetna, Inc
Albany, NY

Dr Kolodziej is the national medical director of oncology solutions, Office of the Chief Medical Officer, Aetna. He attended college and medical school at Washington University in St. Louis where he was Phi Beta Kappa and Alpha Omega Alpha. He completed internal medicine and hematology-oncology training at the University of Pennsylvania in Philadelphia. After completing training, Dr Kolodziej joined the faculty at the University of Oklahoma School of Medicine where he was an associate professor.

He joined New York Oncology in the winter of 1998 and was a partner in the practice until December 2012. He was an active member of the US Oncology Pharmacy and Therapeutics Committee, having served on the executive committee from 2002-2011, and chairman from 2004-2011. He served as medical director for oncology services for US Oncology from 2007-2011. In this role, he helped direct the implementation of the United States Oncology Network (USON) clinical pathways initiative, the integration of the USON electronic medical record into this program, and the development of the USON disease-management and advanced-care planning programs, now known as Innovent Oncology. He has published several manuscripts and given several presentations on oncology care delivery and reimbursement reform, the use of evidence-based treatment to enhance value, and personalized medicine.

Since joining Aetna in January 2013, he has been active in Aetna's oncology delivery reform pilots, pharmacy policy, condition analysis, and genetics subcommittee. He is a fellow of the American College of Physicians and is a member of the board of the Personalized Medicine Coalition. Dr Kolodziej is married to Dr Regina Resta, also a medical oncologist with New York Oncology Hematology; they have 2 children.

Joy Larsen Haidle, MS, CGC

Genetic Counselor
North Memorial Medical Center
Robbinsdale, MN

Ms Haidle is a board-certified genetic counselor at the Humphrey Cancer Center in Robbinsdale, Minnesota, with more than 20 years of experience in counseling hereditary cancer genetics. She is also a policy and peer review consultant

for Blue Cross Blue Shield of Minnesota and an expert resource for other Minnesota Payers. Joy is a clinical preceptor in the Genetic, Cell Biology, and Development Department at the University of Minnesota.

Ms. Larsen Haidle is the president of the National Society of Genetic Counselors. She has a special interest in public policy, appropriate utilization of genetic tests, and identifying individuals/families at increased cancer risk that might benefit from heightened surveillance or risk reduction.

She is recognized nationally for her contributions to the field of genetic counseling, including being the recipient of the National Society of Genetic Counselors Leadership Award: Outstanding Volunteer in 2012. She has coauthored several genetic counseling practice guidelines and has published extensively on a variety of topics including Lynch syndrome and Juvenile polyposis.

Stacey W. McCullough, PharmD

Senior Vice President, Pharmacy
Tennessee Oncology
Murfreesboro, TN

Dr McCullough is the senior vice president, pharmacy for Tennessee Oncology, a large community-based oncology practice. Dr McCullough provides leadership for clinical aspects of drug regimens, overall formulary management, new drug access, and drug purchasing contracts. She also heads up the business development, financial and operations management of Park Pharmacy, Tennessee Oncology's closed door, in-practice, URAC accredited specialty pharmacy.

Dr McCullough is on the pharmacy advisory board (COPA) of Community Oncology Alliance (COA), the charter advisory board of RainTree Oncology Services, VitalSource GPO Advisory Council, as well as, a number pharmaceutical company advisory boards.

Dr McCullough received her Doctor of Pharmacy degree from Auburn University and has been a licensed pharmacist in Tennessee since 1993.

Ted Okon, MBA

Executive Director
Community Oncology Alliance
Washington, DC

Mr Okon is a nationally recognized expert on the policy and politics of cancer care. He is quoted extensively in the press, including guest appearances on TV and radio news shows. Ted has testified before Congress on cancer issues and is frequently on Capitol Hill discussing the nation's cancer care delivery system. His areas of expertise include the cost of cancer treatment, health care reform, Medicare reimbursement, drug shortages, and the changing landscape of cancer care delivery in the United States.

Mr Okon has dedicated his career to health care business and policy. He has worked for several pharmaceutical companies including Merck; Warner Lambert, now part of Pfizer; and IMS Health. He cofounded and took public the health care information business Medical Marketing Group. As executive director of the Community Oncology Alliance (COA), he oversees the strategic direction of this nonprofit organization dedicated to patients and providers in the community cancer care setting, under the direction of a dedicated board of oncologists and practice administrators. He also travels the country speaking to state oncology societies, professional organizations, and companies about the challenges facing the nation's cancer care delivery system. He has authored numerous articles and studies relating to cancer care policy and politics, reimbursement, and clinical issues.

Mr Okon holds a bachelor of science degree from Fairfield University and an MBA from the Carnegie-Mellon University Tepper School of Business. His wife is a full-time practicing oncology nurse.

Kavita Patel, MD

Fellow in Economic Studies and Managing Director
Brookings Institution
Washington, DC

Dr Patel is a practicing primary care internist at Johns Hopkins Medicine. She also served in the Obama Administration as director of policy for the Office of Intergovernmental Affairs and Public Engagement in the White House. As a senior aide to Valerie Jarrett, President Obama's senior advisor, Dr Patel played a critical role in policy development and evaluation of policy initiatives connected to health reform, financial regulatory reform, and economic recovery issues.

Dr Patel also has a deep understanding of Capitol Hill from her time spent on staff with the late US Senator Edward Kennedy, D-Massachusetts. As deputy staff director on health, she served as a policy analyst and trusted aide and was part of the senior staff of the Health, Education, Labor and Pensions (HELP) Committee under Senator Kennedy's leadership. She also has an extensive research and clinical background, having worked as a researcher at the RAND Corporation and as a practicing physician in both California and Oregon. She is a previous Robert Wood Johnson Clinical Scholar, and while at Brookings, she will return to providing clinical care as an internal medicine practitioner. She earned her medical degree from the University of Texas Health Science Center and her master's in public health from the University of California Los Angeles.

Judith R. Peres, LCSW-C

Chevy Chase, MD

Ms Peres is an expert consultant in nursing home and palliative/end-of-life care policy and a clinical social worker serving Medicare beneficiaries. Her policy work uses her expertise at the intersection of palliative-care hospice and long-term services and supports. In her private psychotherapy practice, she works to assist Medicare beneficiaries in navigating the transitions of aging. Her career spans over 4 decades in health policy development and analysis and in direct clinical work. She was selected as a member of the 2013 Institute of Medicine Committee on Approaching Death, which developed the 2014 report *Dying in America,* which outlined recommendations for improving the quality and availability of medical services through the end of life.

In her capacity as a policy consultant, Ms. Peres has worked with the Altarum Institute's Center for Elder Care and Advanced Illness, the Center for Practical Bioethics, and the National Institute of Nursing Research. In addition, she worked for 5 years as an expert consultant in hospice, end-of-life, and palliative care in the Office of Disability, Aging and Long-Term Care in the Office of the Assistant Secretary for Planning and Evaluation (ASPE) at the US Department of Health and Human Services. In her role at ASPE, she managed and developed the *Report to Congress on Advance Care Planning*.

She also served as vice president for policy and advocacy at the former Last Acts Partnership—an initiative of the Robert Wood Johnson Foundation—where she developed major policy pieces such as *Means to A Better End*, the first national report on the state of dying in the United States. Peres also led health policy efforts at the American Association of Homes and Services for the Aging and the Villers Foundation (currently Families USA).

She has served on the Board of Directors of the Social Work Hospice and Palliative Care Network since its inception in 2007. She was a member of the Board of Governors of the Hebrew Home of Greater Washington from 2005-2011. She continues to be involved there and now serves on the Board of Directors through her work on the Strategic Planning Committee. Ms. Peres has a master in social work degree from the University of Maryland and additional training from the Mind/Body Institute in Washington, DC, and in rational emotive behavioral therapy at the Albert Ellis Institute in New York.

Emanuel F. Petricoin III, PhD

Co-Director of the Center for Applied Proteomics and Molecular Medicine
George Mason University
Fairfax, VA

Dr Petricoin has been the co-director of the Center for Applied Proteomics and Molecular Medicine (CAPMM) at George Mason University (GMU) since 2005, where he is also a university professor. Prior to this position, he served as co-director of the FDA-NCI Clinical Proteomics Program and a senior investigator within the Center for Biologics Evaluation and Research at the FDA from 1993-2005. Dr Petricoin received his PhD in microbiology from the University of Maryland in 1990.

The focus of CAPMM is the invention and use of proteomics technologies for personalized therapy and biomarker discovery and measurement for direct clinical applications at the bedside. He is a co-founder of 4 life science companies: Theranostics Health, Inc; Ceres Nanosciences, Inc; C-4 Diagnostics, Inc; and Perthera, Inc. He is a co-inventor on 40 filed and published patents and has authored more than 350 peer-reviewed publications and invited reviews. He has also authored over 40 book chapters; is on the editorial board of *Proteomics, Biomedical Microdevices, Proteomics - Clinical Applications, Proteomics - Protocols, Molecular Carcinogenesis,* and *Journal of Personalized Medicine;* and is a senior editor for *Cancer Epidemiology Biomarkers and Prevention*.

Dr Petricoin is a founding member of the Human Proteomic Organization (HUPO), as well as US HUPO. He has received numerous awards including the university professorship at GMU, the NIH Director's Award, FDA Distinguished Scientist Award, 2015 Innovator of the Year Award, GAP50 Top Virginia Entrepreneurs, Nifty 50 Award, American Society of Cytopathology Basic Research Award, the Roche Diagnostics/CLAS

Distinguished Scientist Award, and the Harvard University Leading Edge Award, and is a Kentucky Colonel.

Bruce Quinn, MD, PhD

Senior Director
FaegreBD Consulting
Washington, DC

Dr Quinn is a national expert on Medicare policy, the impact of health reform on innovation, and the crafting of successful business strategies within the US health care reimbursement system. He has worked successfully with both large and small companies in overcoming hurdles to commercialization through negotiation, understanding insightful ways to use the existing system to their advantage, and the mechanisms of policy change. Since 2008, he has been a full-time business strategist working with attorney and policy teams for health care and life sciences clients.

Dr Quinn travels nationwide to speak on health reform issues and publishes actively, recently writing several peer reviewed policy articles on advanced diagnostics and a series of authoritative white papers on the 2013/2014 coding reform process for genomic tests. Before joining FaegreBD Consulting, Dr Quinn was the regional Medicare medical director for the California Part B program, with authority for final coverage decisions for approximately 15% of the US Medicare program. He later served as senior policy advisor for life sciences clients at Foley Hoag LLP.

Earlier in his career, Dr Quinn was a physician executive in the Health & Life Sciences division of Accenture, working with the pharma, biotech, and genomics industries. He is a board-certified pathologist. As a physician-scientist on the faculty of Northwestern University School of Medicine, Dr Quinn led pathology research for Northwestern's National Institutes of Health-funded Alzheimer Research Center. He has also held academic positions at New York University School of Medicine and the UCLA Center for Health Sciences, and is the author or co-author on over 30 scientific publications.

Bruce Sherman, MD, FCCP, FACOEM

Medical Director
Population Health Management
Cleveland, OH

Dr Sherman is the medical director, population health management, for the RightOpt private exchange offering for Buck Consultants at Xerox. In this role, he provides strategic client support for development, implementation, and ongoing management of integrated, value-based health and performance-management strategies for exchange clients. Additionally, Dr Sherman is the medical director for the Ohio-based Employers Health Coalition, Inc. Previously he was the consulting corporate medical director for Wal-Mart Stores, Inc; Whirlpool Corporation; and The Goodyear Tire & Rubber Company. Dr Sherman has particular interests in the areas of the business value of workforce health and evaluation of quality and efficiency in health care delivery.

Dr Sherman is a member of the leadership board for the Integrated Benefits Institute and holds committee leadership roles with the National Committee for Quality Assurance and Population Health Alliance. A speaker at both the local and national levels, he has presented workforce health and performance-management strategies to diverse audiences and has published numerous related articles. Dr Sherman received his medical from New York University School of Medicine, his master's degree from Harvard University and his bachelor's degree from Brown University. He is board-certified in internal medicine. Dr Sherman continues as a member of the clinical faculty in the Department of Medicine at the Case Western Reserve University School of Medicine.

Glen Stettin, MD

Senior Vice President
Clinical, Research & New Solutions & Chief Innovation Officer
Express Scripts
St. Louis, MO

Dr Stettin leads innovation at Express Scripts, where he is a champion for the patient experience and leader of team of clinicians, behavioral, research and information scientists, and product developers focused on making medicine safer, more effective and more affordable. His areas of responsibility include the Express Scripts Lab, the Therapeutic Resource Centers, Consumerology, research and big data analytics, and product development. Dr Stettin joined Express Scripts in April 2012 with the acquisition of Medco, where was chief medical officer. Over the course of his 17 years leading innovation and change at Medco, Glen served in leadership roles in clinical, operations, technology and product organizations. Dr Stettin is board certified in internal medicine and completed his residency in internal medicine at the University of California, San Francisco, where he also served as medical chief resident, Moffitt-Long Hospital, fellow in cardiology and Robert Wood Johnson Foundation Clinical Scholar at UCSF and Stanford University. He earned his bachelor and medical degrees through a joint program of Lehigh University and the Medical College of Pennsylvania.

Burton VanderLaan, MD, FACP

Medical Director, Network Effectiveness
Priority Health
Grand Rapids, MI

Dr VanderLaan is currently medical director at Priority Health, a nonprofit regional health insurer in western Michigan. Before coming to Priority, he served for nearly 10 years as a regional medical director for Aetna, with responsibility for a 17-state area in the Midwest. Other medical leadership positions he has held include president and CEO of the Accord Health Network, a multi-hospital affiliation in the Chicago area, and vice president and medical director for managed care for Blue Cross Blue Shield of Illinois.

Dr VanderLaan received his medical degree from the University of Chicago, completed post-graduate training at the Michael Reese Medical Center in Chicago, and is board-certified in internal medicine and medical oncology. He is a fellow of the American College of Physicians and a member of the American Society of Clinical Oncology. He has served on the board of the Illinois Hospital Association, is a past president of the Institute of Medicine of Chicago, and currently serves on the board of the Michigan Center for Clinical Systems Improvement.

Jack Whelan

Research Advocate/Event Speaker
JackWhelan.com
Andover, MA

Mr Whelan was diagnosed with a rare, incurable blood cancer in 2009. At that time, research indicated a 5-year outlook for symptomatic patients requiring treatment. He now shares his intensely personal and often humorous journey in personalized medicine; he has encountered what he calls relapsed/refractory detours, conflicting signals and biomarkers, inhibiting regulatory roadblocks and potholes in the healthcare system. Using his business communications and research skills from his career as a Wall Street research analyst in information technology (IT) and career sales VP in IT, he now helps bridge the communications gap between life sciences, medical professionals, and patients as a patient advocate, research advocate, and legislative advocate.

Mr Whelan encourages all patients to explore novel targeting agents, many of which are now in clinical trials. Using genetic and genomic information to develop new disease-specific targeted therapeutics might be safer and more effective treatment than conventional chemotherapy. Mr Whelan understands the realities of his blood cancer, as he has repeatedly relapsed and has been refractory to most of the therapies received thus far; however his goal is repeated periods of progression-free survival, during which the promise of science and delivery of successful therapeutics will be achieved. His website is located at **Jack-Whelan.com**.

Yousuf Zafar, MD, MHS

Assistant Professor, Division of Medical Oncology
Duke Cancer Institute
Durham, NC

Dr Zafar is a gastrointestinal medical oncologist and health care delivery researcher. He is also an associate professor of medicine at the Duke Cancer Institute. His research explores ways to improve care delivery for patients with cancer. He has advanced training in health services research and has participated in studies focusing on access to care, cost of care, and comparative effectiveness of care delivery between health systems. His primary area of interest is in cancer treatment–related financial burdens to patients. He has conducted institutional and national studies on how treatment-related costs impact cancer patients' experiences and quality of care. His current work focuses on how the cost of care can drive medical decision making and impact the physician–patient relationship.

Dr Zafar is the focus area leader for Duke Cancer Institute's Healthcare Delivery Research. He is a member of the American Society of Clinical Oncology's Health Disparities Committee and the Alliance for Clinical Trials in Oncology's Health Disparities and Health Outcomes committees. Dr. Zafar's work has been funded by the National Institutes of Health, the American Cancer Society, the HealthWell Foundation, the Duke Cancer Institute, the Duke Clinical Research Institute, and the CALGB Foundation.

AGENDA—THURSDAY, NOVEMBER 19, 2015

Session 1: Genomics in Oncology

Moderator: *Dennis P. Scanlon, PhD*

- Democratization of Precision Therapy: Omics 101 for Payers
  Emanuel Petricoin III, PhD
- Outcomes From Mandatory Genetic Testing and Counseling Programs
  Joy Larsen Haidle, MS, CGC
- **Panel:** The Impact of FDA Regulation on Diagnostics in Oncology
  Scott Gottlieb, MD; Michael A. Kolodziej, MD; Joy Larsen Haidle, MS, CGC; Bruce Quinn, MD, PhD
- **Keynote Address** – *Julie M. Vose, MD, MBA, FASCO*

AGENDA—FRIDAY, NOVEMBER 20, 2015

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

Moderator: *Bruce A. Feinberg, DO*

- **Panel:** Reimbursement Challenges for Oncology Innovations: Who Pays?
  Peter Bach, MD, MAPP; John Fox, MD, MHA; Daniel Klein, MHS; Yousuf Zafar, MD, MHS
- How the President's Precision Medicine Initiative Will Learn from Oncology Practice
  Michael A. Kolodziej, MD
- The Patient Lens on Precision Medicine
  Jack Whelan

Session 3: The Future of Immuno-oncology

Moderator: *Bruce A. Feinberg, DO*

- Are We Close to the Big "C": Cure?
  Joseph Alvarnas, MD
- Evaluation of Options and Outcomes in a "Me Too" Market
  Stacey W. McCullough, PharmD
- **Panel:** The Role of PBMs in Managing High-Cost Treatment Options
  Stacey W. McCullough, PharmD; Bruce W. Sherman, MD, FCCP, FACOEM; Glen D. Stettin, MD

Session 4: Innovations for Patient Centered Care

Moderator: *Dennis P. Scanlon, PhD*

- Updates in Big Data for Oncology: What Are We Learning?
  Robert J. Green, MD
- How Do Patients Define Value in Cancer Care?
  Yousuf Zafar, MD, MHS
- **Panel:** Navigating the Conflict of Personalized Medicine vs. Population Management
  Joseph Alvarnas, MD; Kavita Patel, MD; Burton F. VanderLaan, MD, FACP

Session 5: Accountable Care in Oncology

Moderator: *Dennis P. Scanlon, PhD*

- **Panel:** Evolution of the ACO Model to Meet the Needs of Oncology Patients and Payers
  Scott Gottlieb, MD; Julian Malinak, MHS; Ted Okon, MBA

Personalized Medicine Enters the "Postgenome Revolution"

MARY CAFFREY

Patients have much to gain from the "democratization" of personalized medicine, as scientific advances and new clinical trials improve treatment for those far from major academic centers, according to Emanuel F. Petricoin III, PhD, a co-director of the Center for Applied Proteomics and Molecular Medicine at George Mason University.

EMANUEL F. PETRICOIN, III, PHD

Petricoin opened the 4th annual meeting of Patient-Centered Oncology Care in Baltimore, Maryland, with his talk, "Democratization of Precision Therapy: Omics 101 for Payers." He discussed how the whole way of thinking about cancer is shifting, from looking at how cancer affects organs to how it is regulated by signaling pathways. It's not just about finding the mutated gene in question, he said, but understanding how it regulated at the molecular level.

"We're now entering the postgenome revolution, where we're talking not just about whether or not genomic alterations exist, but are they transcribed into RNA and ultimately into proteins, and phosphoproteins, and metabolites," he said. "These are the business end of the cell."

Trials getting under way, such as the TAPUR (Targeted Agent and Profiling Utilization Registry) study and NCI-MATCH (the National Cancer Institute Molecular Analysis for Therapy Choice study), both aim to use molecular analysis of tumor specimens in patients. NCI-MATCH will add or drop treatments in multiple arms over time, while TAPUR will test drugs that are already commercially available, reaching patients in community settings.

With these developments, Petricoin said, genomics has become a commodity. The good news is that cancer patients in remote locations can have tissue collected and tests done elsewhere—there are companies springing up to speed the process, help make sure the right tests are ordered, and ensure that results get back to oncologists in a timely manner. But a common problem is one of "insufficient material," which demands technology that can examine hundreds of proteins, phosphoproteins, and signaling proteins without much tissue. The National Institutes of Health has developed such a technology, which has been commercialized, he said.

Petricoin described a 2014 article in *Nature* that reported an effort by a bioinformatics team looking at cell lines and multiple inhibitors—transcriptomic, genomic, exome, proteomic. "It was the RPPA (reverse phase protein array) data, the protein data, which showed the best prediction for drug sensitivity, all beyond the genome," he said. "And so we see this manifest in clinical trials where we can look at signaling pathways at the proteomic level."

Clinical trials today are showing that the proteins are the drug targets, and our understanding about alternations at this level is essential, Petricoin said. He discussed several examples of trials in which protein differences were the distinguishing feature for whether a subgroup of patients would respond to a cancer therapy. Going forward, he said, "We have to prospectively validate this, of course, and this is what we're doing with some of the pharmaceutical companies." If a company would normally enroll 1000 patients in a phase 3 clinical trial, using proteomics to identify those likely to respond to a therapy will allow enrollment of a much smaller cohort. "Enrolling 400 is a lot faster than enrolling 1000," and requires less time and money.

"This is extremely important," Petricoin said. He predicted that in the next year or so, some clinical trials will fail because they did not enroll patients this way and "they have not been able to accrue enough patients into the arms that have been genomically categorized. And that's because the incidence rate for these mutations is very small on a population basis."

What's more, Petricoin said, patients who have metastatic breast cancer were shown to have greatly increased progression-free survival when their treatment decisions were based on multi-omic analysis. This kind of analysis can be used in larger trials, and the turnaround for physicians to make finely tuned treatment decisions can be as short as 7 days, he said.

"We're going to be in a position where we're not talking about classification by location (of the cancer tumor), but classification by multi-omic analysis," Petricoin said. "And we're seeing this in trials like TAPUR, which are starting next year, where any oncologist in the community can get tumor profiling and get access now to the drugs. The NCI-MATCH trial is doing the same thing."

"The problem will be the incidence of the cancer genome alterations that are going to drive whether or not these trials are successful," he said. **EBO**

Genetic Counselors Can Weed Out Errors, Ensure Patients Get Needed Tests, Larsen Haidle Says

ANDREW SMITH

Physicians have good reason to feel overwhelmed by the growing number of genetic tests available for their consideration, said Joy Larsen Haidle, MS, CGC, the 2015 president of the National Society of Genetic Counselors (NSGC).

On a typical day, 10 new tests enter the market and begin competing for attention. That's a lot to absorb by any standard, but it's particularly daunting for professionals who are so busy they often cannot perform the most basic step in personalizing treatment: getting a thorough family history from each patient. Fortunately, Larsen Haidle told the audience at the 4th annual meeting of Patient-Centered Oncology Care, genetic counselors can help doctors take full advantage of new discoveries while cutting wasteful expenditures. Counselors perform a wide variety of services, but the most important may be figuring out which patients should get which genetic tests and which patients shouldn't get any tests at all—a process that starts with the documentation of family history.

"Family history, to me, is the low-hanging fruit and is the core foundation of precision medicine," she said, emphasizing the need for a pedigree that stretches back 3 to 4 generations. "As a genetic counselor, when I'm talking about risk assessment, really all I'm referring to is we're reviewing that pattern of cancers that are in the family to determine the likelihood that there is an inherited risk factor that's contributing to what we're seeing. We need to develop a differential gene list so that when we're trying to select among the panel tests and things that are available, we need to make sure that any test that's selected has all of the genes on the differential, and then select the most appropriate person to do the testing. It may not be the person that's sitting right in front of me, it may be actually a relative instead."

In many cases, these thorough family histories find there's no need for genetic testing. Larsen Haidle showed insurance company data indicating that requirements for genetic counseling can reduce the number of inappropriate genetic tests from more than a quarter of all tests performed (which appears to be a rough approximation of the current norm) to well under 5% of all tests. She also cited the experience at ARUP Laboratories in Salt Lake City, which brought in genetic counselors to review the orders its employees received for genetic testing. They found some sort of error in 26% of the orders and saved $720,000 a year by canceling needless test orders and fixing faulty orders.

Counselors can also improve health outcomes by increasing the percentage of patients who get referred for genetic tests that they really do need, said Larsen Haidle, who cited several studies that indicate many patients slip through the cracks. A study of 684 high-risk women found that 90% of the women discussed their family history with providers, but only 20% of the women were referred for the sort of genetic testing their history justified. Counselors are far more likely to make the proper referrals, said Larsen Haidle, who then turned to research on patient adherence.

"When it comes to the uptake of risk-management strategies for individuals who have hereditary breast and ovarian cancer, they had a higher likelihood of being consistent and following through on those strategies after meeting with a genetic professional," she said. "Increased genetic counseling led to a higher rate of having that same information communicated to the rest of the family."

Such benefits may explain why the demand for genetic counseling has grown quickly. The total number of counselors has grown 88% since 2006, and productivity per counselor has grown significantly. Still, Larsen Haidle argued, many doctors could be taking far more advantage of the services that counselors can offer their patients.

"We know that the current system is not working, with 30% of the tests not being ordered appropriately," she said. "It really is imperative that all of us are working together to do a better job." **EBO**

TABLE. Genetic Counselor Review Identifies That 26% of Genetic Test Orders Require Revision

Percent of Misordered Tests	Correction Made After Review by Genetic Counselor
32%	Canceled incorrect test; added appropriate test
22%	Canceled incorrect test
16%	Canceled gene sequencing; added targeted panel
13%	Canceled gene sequencing; added targeted test for familiilia mutation
11%	Canceled incorrect and facilitated send out
5%	Canceled duplicate test order

Diagnostic Testing Is a Wild West of Unknowns, Perils

TONY HAGEN

The problem with FDA involvement in the regulation of molecular diagnostics testing is not only the esoteric science behind them, but also rapid-fire developments that can make slow-moving FDA decisions irrelevant by the time they arrive.

That's what a group of experts shared during a panel discussion during the 4th annual meeting of Patient-Centered Oncology Care, held in Baltimore, Maryland, by *The American Journal of Managed Care*.

"The FDA does not have a good way to solve for these challenges right now," said Scott Gottlieb, MD, former FDA deputy commissioner for medical and scientific affairs. Gottlieb recalled that during one period of HIV resistance testing, the FDA was looking at genomic tests and eventually would give an approval, but the tests would be obsolete before anybody could come in for testing. "Doctors realized that these tests changed all the time. Genomics changed as the viruses mutated," Gottlieb recalled.

The panel discussion was timely—it took place a few weeks after FDA released a report on why it feels more regulatory oversight of laboratory testing is necessary, basing its conclusions on 20 case studies of problematic outcomes. "Laboratory developed tests (LDTs) serve an increasingly important role in healthcare today. They also have become significantly more complex and higher risk, with several notable examples of inaccurate tests placing patients at otherwise avoidable risk," the report stated in its executive summary.

With a plethora of commercial testing companies and academic laboratories involved in their development, physicians and patients need clear guidance about what they are getting when they order these tests. However, the FDA still needs to make clear what role it plays as a review body—whether it will weigh in on clinical validity or clinical utility, the panelists said.

"The customers need to be confident that the product they're getting and buying is something they can use to make an intelligent decision," said Michael A. Kolodziej, MD, Aetna's national medical director for oncology strategy. "A lot of people do not believe that is occurring. When an oncologist orders the test, they have no idea where it's going and whether it's being done well. Pa-

From left, panelists Scott Gottlieb, MD; Michael Kolodziej, MD; Joy Larsen Haidle, MS, CGC share a light moment during the discussion.

tients would be horrified by that statement. Payers do not have the expertise to look at all of these very complicated molecular tests. We need some kind of proficiency testing. Is the test being done right? That's clinical validity."

Nevertheless, genomic testing is well established by now. There are 155 biomarkers listed on FDA drug labels, according to session moderator Dennis P. Scanlon, PhD, professor of health policy and administration at Penn State University. "Fifty percent of all cancer treatments in early clinical development rely on biomarker data," he noted, and despite the problems associated with genomic testing, the value is indisputable. Women with breast cancer who undergo genetic testing of their tumor prior to treatment enjoy a 34% potential reduction in chemotherapy, he said.

Numerous other issues are associated with this form of diagnostics, including establishing utility for patients, the panelists said. Tissue samples might sometimes be inadequate and a large percentage, upward of 30%, are returned as unacceptable by laboratories; but also, matching tests with patients is a tricky business, and large numbers of tests are performed without true merit, panelists said.

"A key question comes back to what is the test designed to do, and are we selecting the right test?" said panelist Joy Larsen Haidle, MS, CGC, president of the National Society of Genetic Counselors. "We may be getting an accurate result, but the test may not have been designed for that particular patient," she said. "From the patient's perspective, they have to be able to count on that result. It impacts not just them but their families, too."

Another side of this problem is that biomarker testing is very prejudicial to large segments of the patient population, meaning that especially when recruiting for clinical trials, it's hard to assemble a patient cohort that meets the specific requirements of biomarker expression at the molecular level. "A drumbeat of trials that are failing is predicted because they haven't been able to accumulate enough patients," Scanlon said. "This incidence rate is really the elephant in the room. Various trials have already run into this issue."

The US genomics testing market was estimated at $5.9 billion in 2011 by research firm Booz Allen Hamilton, with nearly 2900 different tests available in that year. Subsequent research released in June by Grand View Research predicted that the genomics testing market just in the United States would hit $27.87 billion by 2022.[1]

With this scale of growth and marketing in mind, the FDA has been working to develop a set of standards and processes to ensure that the tests are reliable. The agency is also working to develop clinical databases that will help physicians make better clinical decisions based on the test results.

"There are a lot of ways to make errors in sequencing, and our concept is to develop a set of process and material standards that will, we hope, allow us to essentially be confident that a lab that develops a test will do it in a manner that generates a test that is accurate and reliable," Elizabeth Mansfield, PhD, director of personalized medicine for the FDA, said in an interview earlier this year.

In its report issued in November, the FDA stated that it examined events involving 20 laboratory developed tests (LDT) "that illustrate, in the absence of compliance with FDA requirements, that these products may have caused or have caused actual harm to patients. In some cases, due to false-positive tests, patients were told they have conditions they do not really have, causing unnecessary distress and resulting in unneeded treatment. In other cases, the LDTs were prone to false-negative results, in which patients' life-threatening diseases went undetected. As a result, patients failed to receive effective treatments."[2]

> **"A key question comes back to what is the test designed to do, and are we selecting the right test? We may be getting an accurate result, but the test may not have been designed for that particular patient. From the patient's perspective, they have to be able to count on the result. It impacts not just them but their families, too."**
>
> —JOY LARSEN HAIDLE, MS, CGC, NATIONAL SOCIETY OF GENETIC COUNSELORS, 2015 PRESIDENT

"Other LDTs provided information with no proven relevance to the disease or condition for which they are intended for use, while still others are linked to treatments based on disproven scientific concepts. In addition to patient harm, inaccurate or unreliable tests can be costly to society," the report stated.[2]

While the FDA has taken a relatively passive role in oversight of LDT, the Clinical Laboratory Improvement Amendments (CLIA) from CMS do provide standards, and yet all of the problem tests discussed in the FDA report did follow

An attendee at Patient-Centered Oncology Care asks a question during the panel discussion on diagnostic testing.

CLIA recommendations, which contributes to the conclusion that CLIA may not be strong enough, the FDA said. It said CLIA fails to ensure safety and effectiveness of tests prior to marketing and that it makes no assessment of the quality and design of testing devices.

"Greater FDA oversight is needed to promote access to LDTs that provide benefits to patients and the health care system, while helping to ensure patients are not unduly exposed to harm," the report concluded.

Still, the federal government may be overreaching if it takes on too big of a role as a watchdog when it comes to genomics testing, Gottlieb said. "There's a lot of tools. Some are used appropriately and some are not. Some information is used appropriately and not. But it's very risky to put a government arbiter in the position of making a determination."

If the government is reluctant or hamstrung in its ability to step in and provide the necessary oversight and guidance, the burden must fall to the professional societies that care deeply about the results and can be relied on to develop standardized procedures, said Kolodziej. "There's an opportunity now, if the government won't do it, for the professional societies to do it. Payers actually pay attention to what the professional societies say. The NCCN has tremendous influence."

His thought was seconded by panelist Bruce Quinn, MD, PhD, MBA, senior director of FaegreBD Consulting in Washington, DC, who specializes in Medicare policy and health reform in innovation. "Professional societies are extremely important in determining where the cut points should be," he said.

Whereas, confusion appears to reign in this burgeoning field of medical diagnostics, there is a rapidly growing presence of certified genetic counselors (CGCs) who function as in-betweens to directly guide patients toward informed use of genetic testing. They supplement the expertise of doctors for whom these diagnostics may outstrip their zone of competence, said Larsen- Haidle. There has been an 88% increase in CGCs since 2006, she added.

Their skills are brought to bear in a variety of forums, Larsen-Haidle said, among them face-to-face consulting, telephone and computer interaction, and rural settings. Genetic counselors can reduce costs to the healthcare system by reducing inappropriate testing, she said, adding that through their expertise and particular focus, they can detect genetic risk factors in patients whom referring providers may fail to detect. **EBO**

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ASCO President Reviews Post-SGR Challenges for Oncologists

SURABHI DANGI-GARIMELLA, PHD

At Patient-Centered Oncology Care 2015, hosted by *The American Journal of Managed Care* in Baltimore, Maryland, keynote speaker Julie M. Vose, MD, MBA, FASCO, president of the American Society of Clinical Oncology (ASCO) provided perspectives on the challenges faced by oncologists as the healthcare system transitions to define and incorporate value in the care delivered.

"Unfortunately, there is an administrative burden that physicians have to bear and so there's not much time to spend with the patient," she said, adding, "We have to take this back to the patient and physicians need to ensure that they don't just turn into data-entry operators," hinting at the growing administrative burden faced by physicians.

Achieving the triple aim of better care, improved heath, and lower costs—all in a value-based manner—are a physician's goals, "But how do we get there?" asked Vose. She indicated that the answer is enveloped in multiple layers:

- We need to make sure evidence-based practices are followed
- Available resources should be used efficiently
- Quality measures and improvement are vital
- Practices need adequate support to avoid duplication of efforts and improve patient engagement, in order to provide better care in a value-based manner
- Oncology is based on innovation and new treatments should be value-based.

Pointing to CMS' emphasis on transitioning from the fee-for-service (FFS) to value-based care, Vose said that FFS drives volume without necessarily ensuring quality. "The administration has set an ambitious goal of at least 50% of all Medicare payments based on alternative payment models by 2018. I don't think this is possible by 2018 though," she said.

JULIE M. VOSE, MD, MBA, FASCO

Vose emphasized that patient care should achieve the highestvalue level. "Cost and toxicity should be incorporated into the value proposition and we need to move beyond process measures and ensure outcomes improve with the value-based changes," she added (**FIGURE 1**).

Most quality measures today are process-based, said Vose, and pointed to ASCO's QOPI project (Quality Oncology Practice Initiative) that allows for performance measurement and feedback. In addition to process measures, QOPI site visits ensure meeting QOPI certification. Additionally, mentorship programs allow data exchange and further help dissipate the model, she said.

How has ASCO improved on these essential requirements?

It's been a multi-pronged approach through the efficient use of *Choosing Wisely*; PracticeNet, a suite of services to allow value-based care and improve clinic practices; and team-based care, which is extremely important, especially with the increased need for oncologists as the rate of patients with cancer rises.

Vose then explained that ASCO's Value Framework has tried to incorporate all of these factors: shared decision-making, added benefit vs existing therapy, meeting individual patient goals and circumstances.

She talked about the Merit-Based Incentive Payment System (MIPS), which came into being after Medicare Authorization and CHIP Reauthorization Act or MACRA replaced the Sustainable Growth Rate (SGR), a big step forward, but, thus, has created new needs. This would bring about a significant change and create a big opportunity to improve patient care. Physicians can use MIPs or alternative payment models—a new way to look at performance measurement. However, public reporting that pits physicians against one another represents a big change, and it will take time to adapt.

"Although the SGR is gone, we are still cutting up one pie. The size of positive updates or bonuses depends on how many people get penalties for not performing. This is new. And scary," Vose added.

MIPS will significantly impact the physician payment program in terms of dollar cost, she said, in primarily 4 domains: resource use, quality reporting, HER, and clinical improvement activities. "The information will be collected, beginning 2017, to be implemented in 2019. We need tools to help with gap in care coordination that don't currently exist," Vose added.

Oncologists, though, are feeling unprepared. "While the goals providers have been striving to meet are still the same, such as meeting national benchmarks for quality in the form of performance measures, making use of EHRs, continually improving our clinical care, and doing it in the most efficient way possible, challenges remain." Measurement tools remain the major challenge.

"And MACRA comes at a time when there is already significant turbulence in the oncology practice community," Vose emphasized.

Oncologists face a lot of practice pressures, and they vary based on physician-owned community practices, academic, or health centers, (**FIGURE 2**). "Smaller practices are our special concern; they are the backbone of the US oncology care delivery system. But the current trend is toward consolidation, which is modifying the face of oncology."

Information overload is not helping oncologists either, whether it be clinical information or administrative adaptations with new rulings and requirements. "There are also administrative overloads; we know of a practice that had 8 different clinical pathways for each of the payers they worked with."

Indicating that APMs can help achieve transformation, Vose said that ASCO's patient-centered oncology payment model tries to match support with the work being done to avoid cost-shifting to patients. "It's a big collaborative project and we plan to data-share to get feedback for improvement," Vose said.

How do we agree on improving on pathways and value measures?

While rapid-learning systems would improve efficiency of care, there are challenges that need to be met:

1. Need new ways to test drugs per tumor's molecular characteristics, eg, NCI-MATCH, TAPUR
2. Learn from every patient (irrespective of trial participation)
3. Harness data in powerful new ways.

"The patient needs to be the center of what we are doing: improve outcomes, reduce side effects and do this in a value-based manner. We need to harness our collective wisdom as we do this," Vose said. **EBO**

FIGURE 1. Ensuring Patient-Centered Care

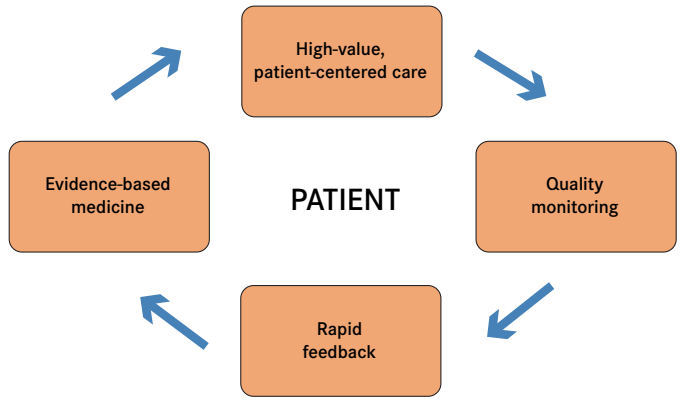
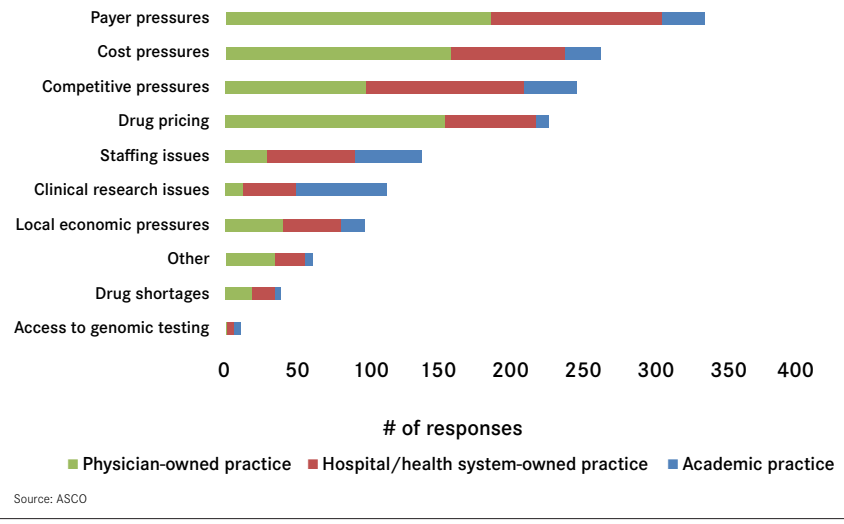


FIGURE 2. Practice Pressures



Source: ASCO

THE AMERICAN JOURNAL OF MANAGED CARE

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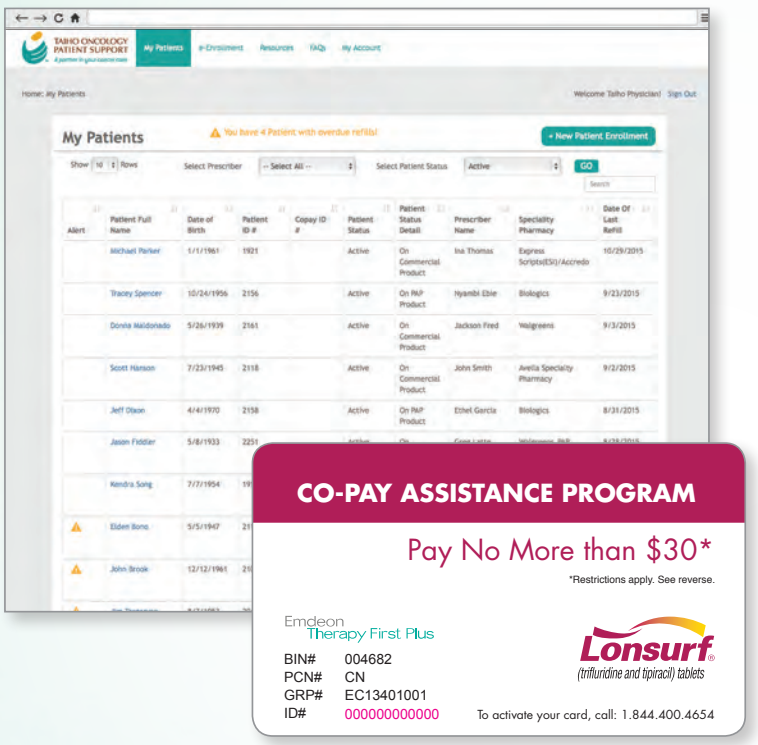

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Please see Important Safety Information and brief summary of Prescribing Information on the following pages.

Lonsurf® (trifluridine and tipiracil) tablets

TAIHO ONCOLOGY

Lonsurf®
(trifluridine and tipiracil) tablets

Indication

LONSURF is indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if *RAS* wild type, an anti-EGFR therapy.

Important Safety Information

WARNINGS AND PRECAUTIONS

Severe Myelosuppression: In Study 1, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%), and febrile neutropenia (3.8%). One patient (0.2%) died due to neutropenic infection. In Study 1, 9.4% of LONSURF-treated patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for febrile neutropenia, Grade 4 neutropenia, or platelets less than 50,000/mm^3. Upon recovery, resume LONSURF at a reduced dose.

Embryo-Fetal Toxicity: LONSURF can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF.

USE IN SPECIFIC POPULATIONS

Lactation: It is not known whether LONSURF or its metabolites are present in human milk. There are no data to assess the effects of LONSURF or its metabolites on the breast-fed infant or the effects on milk production. Because of the potential for serious adverse reactions in breast-fed infants, advise women not to breast-feed during treatment with LONSURF and for 1 day following the final dose.

Male Contraception: Advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose.

Geriatric Use: Grade 3 or 4 neutropenia and thrombocytopenia and Grade 3 anemia occurred more commonly in patients 65 years or older who received LONSURF.

Renal Impairment: Patients with moderate renal impairment may require dose modifications for increased toxicity. No patients with severe renal impairment were enrolled in Study 1.

Hepatic Impairment: Patients with moderate or severe hepatic impairment were not enrolled in Study 1.

ADVERSE REACTIONS

Most Common Adverse Drug Reactions in Patients Treated With LONSURF (≥5%): The most common adverse drug reactions in LONSURF-treated patients vs placebo-treated patients with refractory mCRC, respectively, were asthenia/fatigue (52% vs 35%), nausea (48% vs 24%), decreased appetite (39% vs 29%), diarrhea (32% vs 12%), vomiting (28% vs 14%), abdominal pain (21% vs 18%), pyrexia (19% vs 14%), stomatitis (8% vs 6%), dysgeusia (7% vs 2%), and alopecia (7% vs 1%).

Additional Important Adverse Drug Reactions: The following occurred more frequently in LONSURF-treated patients compared to placebo: infections (27% vs 15%) and pulmonary emboli (2% vs 0%).

Interstitial lung disease (0.2%), including fatalities, has been reported in clinical studies and clinical practice settings in Asia.

Laboratory Test Abnormalities in Patients Treated With LONSURF: Laboratory test abnormalities in LONSURF-treated patients vs placebo-treated patients with refractory mCRC, respectively, were anemia (77% vs 33%), neutropenia (67% vs 1%), and thrombocytopenia (42% vs 8%).

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

Learn more at LONSURFhcp.com

TAIHO ONCOLOGY

LONSURF (trifluridine and tipiracil) tablets, for oral use
Initial U.S. Approval: 2015

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

1 INDICATIONS AND USAGE
LONSURF is indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Severe Myelosuppression
In Study 1, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%) and febrile neutropenia (3.8%). One patient (0.2%) died due to neutropenic infection. In Study 1, 9.4% of LONSURF-treated patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on Day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for febrile neutropenia, Grade 4 neutropenia, or platelets less than 50,000/mm^3. Upon recovery resume LONSURF at a reduced dose. *[see Dosage and Administration (2.2) in the full Prescribing Information]*

5.2 Embryo-Fetal Toxicity
Based on animal studies and its mechanism of action, LONSURF can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dose levels resulting in exposures lower than those achieved at the recommended dose of 35 mg/m^2 twice daily.

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF. *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1) in the full Prescribing Information]*

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

The data described below are from Study 1, a randomized (2:1), double-blind, placebo-controlled trial in which 533 patients (median age 63 years; 61% men; 57% White, 35% Asian, 1% Black) with previously treated metastatic colorectal cancer received LONSURF as a single agent at a dose of 35 mg/m^2/dose administered twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. The mean duration of LONSURF therapy was 12.7 weeks.

The most common adverse drug reactions or laboratory abnormalities (all Grades and greater than or equal to 10% in incidence) in patients treated with LONSURF at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

In Study 1, 3.6% of patients discontinued LONSURF for an adverse event and 13.7% of patients required a dose reduction. The most common adverse reactions leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

Table 1 Per Patient Incidence of Adverse Drug Reactions (≥5%) in Study 1 Occurring More Commonly (>2%) than in Patients Receiving Placebo.

Adverse Reactions	LONSURF (N=533)		Placebo (N=265)	
	All Grades	Grades 3-4*	All Grades	Grades 3-4*
Gastrointestinal disorders				
Nausea	48%	2%	24%	1%
Diarrhea	32%	3%	12%	<1%
Vomiting	28%	2%	14%	<1%
Abdominal pain	21%	2%	18%	4%
Stomatitis	8%	<1%	6%	0%
General disorders and administration site conditions				
Asthenia/fatigue	52%	7%	35%	9%
Pyrexia	19%	1%	14%	<1%
Metabolism and nutrition disorders				
Decreased appetite	39%	4%	29%	5%
Nervous system disorders				
Dysgeusia	7%	0%	2%	0%
Skin and subcutaneous tissue disorders				
Alopecia	7%	0%	1%	0%

*No Grade 4 definition for nausea, abdominal pain, or fatigue in National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

Table 2 Laboratory Test Abnormalities

Laboratory Parameter	LONSURF (N=533*)			Placebo (N=265*)		
	Grade†			Grade†		
	All %	3 %	4 %	All %	3 %	4 %
Blood and lymphatic system disorders						
Anemia‡	77	18	N/A#	33	3	N/A
Neutropenia	67	27	11	1	0	0
Thrombocytopenia	42	5	1	8	<1	<1

*% based on number of patients with post-baseline samples, which may be less than 533 (LONSURF) or 265 (placebo)
† Common Terminology Criteria for Adverse Events (CTCAE), v4.03
‡ Anemia: No Grade 4 definition for these laboratory parameters in CTCAE, v4.03
# One Grade 4 anemia adverse reaction based on clinical criteria was reported

In Study 1, infections occurred more frequently in LONSURF-treated patients (27%) compared to those receiving placebo (15%). The most commonly reported infections which occurred more frequently in LONSURF-treated patients were nasopharyngitis (4% versus 2%), and urinary tract infections (4% versus 2%).

In Study 1, pulmonary emboli occurred more frequently in LONSURF-treatment patients (2%) compared to no patients on placebo.

Additional Clinical Experience
Interstitial lung disease was reported in fifteen (0.2%) patients, three of which were fatal, among approximately 7,000 patients exposed to LONSURF in clinical studies and clinical practice settings in Asia.

7 DRUG INTERACTIONS
No pharmacokinetic drug-drug interaction studies have been conducted with LONSURF.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Based on animal data and its mechanism of action, LONSURF can cause fetal harm. LONSURF caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation at doses resulting in exposures lower than or similar to exposures at the recommended dose in humans. [see *Data*] There are no available data on LONSURF exposure in pregnant women. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Trifluridine/tipiracil was administered orally once daily to female rats during organogenesis at dose levels of 15, 50, and 150 mg/kg [trifluridine (FTD) equivalent]. Decreased fetal weight was observed at FTD doses greater than or equal to 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m^2 twice daily). At the FTD dose of 150 mg/kg (approximately 0.92 times the FTD exposure at the clinical dose of 35 mg/m^2 twice daily) embryolethality and structural anomalies (kinked tail, cleft palate, ectrodactyly, anasarca, alterations in great vessels, and skeletal anomalies) were observed.

8.2 Lactation

Risk Summary

It is not known whether LONSURF or its metabolites are present in human milk. In nursing rats, trifluridine and tipiracil or their metabolites were present in breast milk. There are no data to assess the effects of LONSURF or its metabolites on the breastfed infant or the effects on milk production. Because of the potential for serious adverse reactions in breastfeeding infants, advise women not to breastfeed during treatment with LONSURF and for one day following the final dose.

Data

Radioactivity was excreted in the milk of nursing rats dosed with trifluridine/tipiracil containing ^{14}C-FTD or ^{14}C-tipiracil (TPI). Levels of FTD-derived radioactivity were as high as approximately 50% of the exposure in maternal plasma an hour after dosing with trifluridine/tipiracil and were approximately the same as those in maternal plasma for up to 12 hours following dosing. Exposure to TPI-derived radioactivity was higher in milk than in maternal plasma beginning 2 hours after dosing and continuing for at least 12 hours following administration of trifuridine/tipiracil.

8.3 Females and Males of Reproductive Potential

Contraception

Females

LONSURF can cause fetal harm when administered to a pregnant woman. *[*see *Use in Specific Populations (8.1)]*

Advise females of reproductive potential to use effective contraception during treatment.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose. *[*see *Nonclinical Toxicology (13.1) in the full Prescribing Information]*

8.4 Pediatric Use

Safety and effectiveness of LONSURF in pediatric patients have not been established.

Animal Data

Dental toxicity including whitening, breakage, and malocclusion (degeneration and disarrangement in the ameloblasts, papillary layer cells and odontoblasts) were observed in rats treated with trifluridine/tipiracil at doses greater than or equal to 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m^2 twice daily).

8.5 Geriatric Use

In Study 1, 533 patients received LONSURF; 44% were 65 years of age or over, while 7% were 75 and over. No overall differences in effectiveness were observed in patients 65 or older versus younger patients, and no adjustment is recommended for the starting dose of LONSURF based on age.

Patients 65 years of age or older who received LONSURF had a higher incidence of the following compared to patients younger than 65 years: Grade 3 or 4 neutropenia (48% vs 30%), Grade 3 anemia (26% vs 12%), and Grade 3 or 4 thrombocytopenia (9% vs 2%).

8.6 Hepatic Impairment

No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of LONSURF. No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin (TB) less than or equal to the upper limit of normal (ULN) and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST). Patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment were not enrolled in Study 1. *[*see *Clinical Pharmacology (12.3) in the full Prescribing Information]*

8.7 Renal Impairment

No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of LONSURF.

In Study 1, patients with moderate renal impairment (CLcr = 30 to 59 mL/min, n= 47) had a higher incidence (difference of at least 5%) of ≥ Grade 3 adverse events, serious adverse events, and dose delays and reductions compared to patients with normal renal function (CLcr ≥ 90 mL/min, n= 306) or patients with mild renal impairment (CLcr = 60 to 89 mL/min, n= 178).

No dose adjustment to the starting dose of LONSURF is recommended in patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min); however patients with moderate renal impairment may require dose modification for increased toxicity. No patients with severe renal impairment (CLcr < 30 mL/min) were enrolled in Study 1. *[*see *Clinical Pharmacology (12.3) in the full Prescribing Information]*

8.8 Ethnicity

There were no clinically meaningful differences in Study 1 between Western and Asian subgroups with respect to overall incidence of adverse events or ≥ Grade 3 adverse events in either the LONSURF or placebo groups.

10 OVERDOSAGE

The highest dose of LONSURF administered in clinical studies was 180 mg/m^2 per day.

There is no known antidote for LONSURF overdosage.

17 PATIENT COUNSELING INFORMATION

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

Severe Myelosuppression:

Advise the patient to immediately contact their healthcare provider if they experience signs or symptoms of infection and advise patients to keep all appointments for blood tests. *[*see *Warnings and Precautions (5.1)]*

Gastrointestinal toxicity:

Advise patients to contact their healthcare provider for severe or persistent nausea, vomiting, diarrhea, or abdominal pain. *[*see *Adverse Reactions (6.1)]*

Administration Instructions:

Advise the patient that LONSURF is available in two strengths and they may receive both strength tablets to provide the prescribed dose. Advise the patient of the importance of reading prescription labels carefully and taking the appropriate number of tablets.

Advise the patient to take LONSURF within 1 hour after eating their morning and evening meals. *[*see *Dosage and Administration (2.1) in the full Prescribing Information]*

Advise the patient that anyone else who handles their medication should wear gloves. *[*see *References (15) in the full Prescribing Information]*

Embryo-Fetal Toxicity:

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF. *[*see *Warnings and Precautions (5.2)* and *Use in Specific Populations (8.3)]*

Lactation:

Advise women not to breastfeed during treatment with LONSURF and for one day following the final dose. *[*see *Use in Specific Populations (8.2)]*

TAIHO ONCOLOGY, INC.

As Prospect of Risk for Doctors Looms, Cost Conversation Shifts in Cancer Care

MARY CAFFREY

More than 3 years have passed since the famous episode at Memorial Sloan Kettering Cancer Center, when the pharmacy committee's oncologists told Peter S. Bach, MD, MAPP, that they would not put the colorectal cancer drug Zaltrap on the hospital's formulary. It cost twice as much as a similar drug and offered no real advantage. An op-ed that Bach wrote with 2 fellow physicians for *The New York Times* forced Zaltrap's manufacturer to cut its price—and kicked off a national conversation about the cost of cancer drugs that continues to this day.

PETER S. BACH, MD, MAPP

That discussion continued when Bach joined the panel, "Reimbursement Challenges for Oncology Innovations: Who Pays?" which opened the second day of Patient-Centered Oncology Care 2015, presented by *The American Journal of Managed Care* in Baltimore. Also taking part were S. Yousuf Zafar, MD, MHS, an oncologist and health services expert at Duke Cancer Institute, who studies the cost of cancer care; John Fox, MD, MHA, senior medical director and associate vice president for medical affairs at Priority Health; and Dan Klein, MHS, president and CEO of the Patient Access Network Foundation, which helps patients fund co-payments for expensive specialty therapies. Bruce Feinberg, DO, an oncologist and chief medical officer at Cardinal Health Specialty Solutions, served as moderator.

Since the Zaltrap episode, Bach has introduced the DrugAbacus" an online tool to help patients think about a drug's value. Both the American Society of Clinical Oncology and the National Comprehensive Cancer Network have introduced value calculators. Discussions of cost, once off-limits for doctors, are considered essential when it's clear that a 6-figure therapy will only offer a few weeks, perhaps months, of life.

But that doesn't mean that doctors enjoy having those conversations, Zafar said. "As an oncologist who's interested in value, I'm in a really interesting position," he said, describing how he's found himself in the clinic prescribing drugs he knows will offer marginal value.

When it comes to discussing cost and value of cancer drugs, he said, "There's 2 conversations." "First, you think about the value to society…we love the idea of performance-based coverage. But there's that second discussion in the clinic, where I've got to put some of that out of my mind as I discuss the cost with the patient."

Like many other physicians, Zafar said, he finds himself having to address cost. "But we weren't trained to do that. It's our job to protect the patient from harm." The definition of "harm" is shifting, however. Zafar's own research, and that of others, shows that patients with cancer experience financial stress that leads to other problems, which can include poor adherence to oral therapies they take at home.

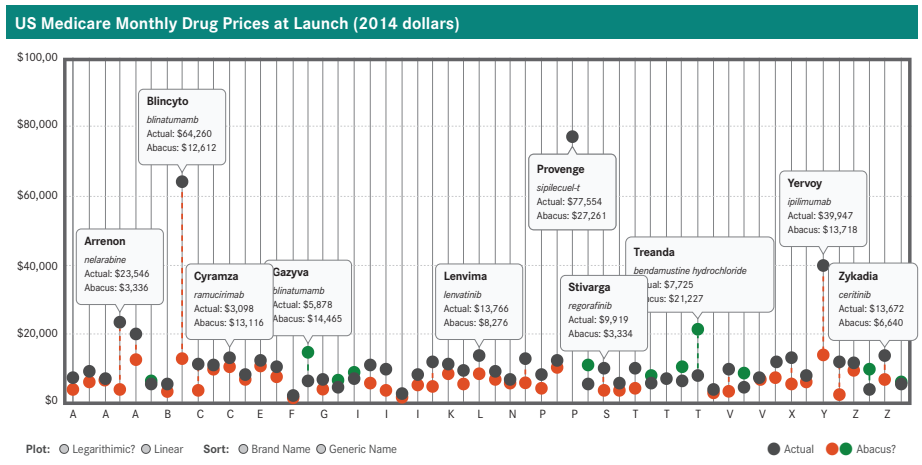
RULES OF THE MARKET DON'T APPLY

"I come from a market-oriented background, and for some period of time, I believed that we could get the market to function," said Bach, as he started the discussion of what's happened to cancer drug prices. "It doesn't seem to be working out that way." He described how many have used the example of the different hepatitis C drugs—how Sovaldi came on the market at $1000 a pill, but once the drug had competition, pharmacy benefit managers were able to strike exclusivity deals to pay much less. That doesn't really apply in cancer care, Bach said.

DAN KLEIN, MHS

Drug development is advancing quickly, so substitutions aren't always possible. In addition, drugs that have been on the market for years keep rising in price. Bach cited the example of Gleevec, a standard treatment for forms of leukemia, which he said has gone up in price 5% each year, except for a 1-time 2% drop when a competitor reached the market. When it comes to cancer therapy, he said, "We have too few purchasers and too few providers."

Fox, the payer on the panel, introduced the idea of paying for outcomes. "We pay a lot of money for drugs that aren't appropriate and don't work," he said. Payers would welcome relationships with drug manufacturers who would agree to prices based on whether the drug worked, not "whatever price they demand."



A view of the DrugAbacus developed by Memorial Sloan Kettering Cancer Center, which can be found at drugabacus.org.

WHAT'S THE ROLE OF THE PATIENT?

Feinberg asked whether patients are capable of taking an active role in shared decision-making about value. "Is it too much of a burden?" he asked.

Klein said that a conversation about value implies there are high- and low-cost options, but that that's not always true. "In oncology or hepatitis C, there aren't always substitutions available, so it's not a fair questions to ask," he said.

Today, an insured patient typically still has plenty to pay out-of-pocket. The Affordable Care Act has given millions health coverage, but Klein said many individuals with modest incomes also have high deductibles and co-insurance and drugs in the specialty tiers can have high cost-sharing for cancer or hepatitis C.

The Patient Access Network (PAN) Foundation exists because too many people could not gain access to innovative therapies, even with insurance. "PAN plays a role that no one else fills," he said. Some have asked whether patients truly feel the burden when a charity helps pay part of their costs, but Klein says that's absurd. "The deductibles and co-pays are so high, it's not even a question of a moral hazard anymore." For a patient on Medicare earning 200% of the federal poverty line, they're spending 15% of their income "just to get through the donut hole," he said.

"SKIN IN THE GAME"

Fox wondered whether choices about therapies would change as reimbursement formulas shift, requiring physicians to assume more financial risk. "What decisions will physicians make when they have some skin in the game?"

Feinberg, and then Bach, raised the possibility that there might be an incentive to withhold therapy in some cases, just as some wonder if physicians have incentives to prescribe too much under the "buy-and-bill" formula that exists today.

Zafar said incentives and disincentives work today, but not always in the way people think. "I see it every day. The vast majority of the community oncologists are treating patients the way they need to be treated," he said. There have been times when a community oncologist has referred a patient to Duke, because the small practice could not afford to cover an expensive medication a patient needed. Zafar has been told, "Duke's going to cover it."

If there's more focus on what patients want, Fox said, he believes more attention will be paid to palliative care. "We need to understand what patients want, what families want, and eliminate what patients and families don't want."

Bach returned to a theme that set off the national conversation: the drug prices are simply too high. "Oncology is the only sector where the manufacturers set their own price," he said. **EBO**

Kolodziej on Precision Medicine: *Standardization, Transparency Needed in Data Collection*

ANDREW SMITH

Targeted treatment regimens have certainly enjoyed considerable success, but Michael Kolodziej, MD, FACP, sees major systemic problems in the ways we analyze tumors, choose therapies, and collect the data that should drive improvement.

Kolodziej is Aetna's national medical director for oncology strategies. However, as he took the stage on the second day of the 4th annual meeting of Patient-Centered Oncology Care to discuss current problems with and possible fixes for precision medicine, he noted the views presented were his own and not those of his employer.

MICHAEL KOLODZIEJ, MD, FACP

Problems with the current system begin the moment a physician decides to send a patient's tumor out for genetic testing, Kolodziej said. Different companies often use different techniques to evaluate mutations in any given gene, and neither the physicians nor anyone else has much idea which methodology is best: are lightly-regulated testing companies executing their chosen methodologies competently or do third-party tests provide the same information as companion diagnostics? Worse, he continued, when results indicate a mutation in a relevant gene, they often fail to provide context that could help caregivers make wise decisions. Test results often fail to specify if a particular mutation is actually in the tumor or how common it is in the tumor. Moreover, gaps in research often leave physicians no way of knowing whether a particular mutation alters tumor function or whether they should use a different regimen if the mutation is expressed in 2% versus 82% of all tumor cells.

Kolodziej lamented a tendency to base broad treatment guidelines on relatively narrow trial data and illustrated his point by asserting that the National Comprehensive Cancer Network (NCCN) recommends targeted therapy for too many patients with HER2 mutations. "Outside of breast and GE [gastroesophageal] junction cancer, amplification is not the most common abnormality in HER2; it's actually a point mutation. And actually if you look at the point mutations that occur in HER2, some of them are activating, and some of them are not. So, guess what? If you give Herceptin to a HER2-mutated patient with a nonactivating mutation, it has zero chance of working. Zero," he said.

"I could say that about just about everything on this list," he added, pointing to an NCCN guideline that broadly recommended particular targeted therapies for patients with particular genetic alterations. "Part of our problem is we've dumbed this down too much. We think that if you got a mutation that represents a lock and we got that key and we're going to open it, but that actually turns out not to be the case."

Kolodziej also lamented the unsustainable growth in treatment costs before turning his attention to large studies that could make precision medicine far more precise. He argued, however, that efforts like TAPUR (Targeted Agent and Profiling Utilization Registry) and NCI-MATCH (Molecular Analysis for Therapy Choice) will only provide maximum benefits if their sponsors work together now to ensure that the information they produce is compatible enough for pooled analyses.

Kolodziej hopes that research organizations everywhere will agree on standards that will produce comparable data from similar studies anywhere around the world. He also hopes that regulators will create and enforce standards for data collection and presentation that make every diagnostic test and treatment regimen for patients in a clinical setting available for study.

"Here's what I think the president can do," said Kolodziej. "The testing nomenclature needs to be standardized. Proficiency testing is absolutely mandatory. We need to develop a methodology to curate and validate the catalogue of mutations. We need to put enough money behind basket-and-umbrella trials, which are a good way to try to answer some of these questions. We need a transparent, public access national registry, a rapid learning system. We need to learn from every patient. And most importantly, that data needs to be democratized and transparent. Everybody needs to get access to it. It's not something that you can sell, or at least it shouldn't be." **EBO**

Becoming a More Educated e-Patient

BRENNA DIAZ

Author and advocate, Jack Whelan, recounted his experiences as an individual living with cancer, and stressed the importance of patients' involvement in their treatment during his talk at the 2015 meeting of Patient-Centered Oncology Care.

Whelan was diagnosed with a rare incurable blood cancer—a type of lymphoplasmacytic lymphoma called Waldenstrom macroglobulinemia (WM)—around 2007. His symptoms included exhaustion after any physical exertion, nose bleeds, and some evidence of neuropathy. With an outlook of living 5 more years and no treatment or standard of care available, Whelan decided he would become an e-patient.

Being an e-patient, Whelan uses his electronic connections to educate himself about his condition and become more involved in his healthcare. He believes patients should be educated and equipped to handle their diagnoses, considered equals with their physicians, capable of asking relevant questions, and willing to make choices about their care.

As Whelan was prescribed various drugs during clinical trials, he measured his own biomarkers and noted how he responded to his therapeutics, tracking his disease progression. "[W]hen I saw these relapse periods coming, that's when I could raise my hand, go to my oncologist, and say it's time to move on to another drug," Whelan explained.

During this period of trial and error, Whelan realized the importance of monitoring the data of clinical trials in real-time. Rather than spending excessive time on biomarker analysis, Whelan wants to move away from batch data and examine patient data and responses.

"We need to move those companion diagnostics out into the clinics," he said. "We actually have to test the safety and efficacy of the drug at the time it's given to the patient." In this case, Whelan promotes a genomics-based therapy in order to determine, ahead of time, which drugs will be safer and more effective.

Whelan identified 2 key obstacles in the communication approach of the therapeutics industry, which he considers to be research-centered, rather than patient-centered. First, distribution does not facilitate communication between patients and the therapeutics developers. He suggested refocusing on the patient's experience in order to promote a free flow of information between the patient and the developer, rather than relying on an intermediary. Whelan emphasized that he does not believe patients should decide how everything is done, but he does view them as a valuable component of effective healthcare.

The second obstacle is the industry's prevailing risk-averse attitude, which also hampers the free flow of information. Targeted agents in clinical trials may be safer, and more effective, than conventional chemotherapy, Whelan said, and so regulators should strive to be bolder and move forward.

Another growing issue with the healthcare industry is financial toxicity, Whelan added. There is major discrepancy between medical costs and pharmaceutical costs. A patient may sit in an infusion room for chemotherapy at $50,000 per month and receive 100% coverage, while a patient prescribed a biologic or molecular targeting agent in pill form from a pharmacy at $2813 per month, may only receive 20% to 25% coinsurance. The clinical trials of today place the protocol, lab, and research above the patient, clinic, and treatment.

In order to dramatically reduce the cost of healthcare and drugs, Whelan recommended that the drugs the government purchases for CMS and the Department of Veterans Affairs be made tax-exempt, as the Department of Defense does with their weaponry.

"If you looked at the total NIH [National Institutes of Health] budget and divided it by the population of the US, it's less than $100 per person; yet we spend $8750 per person for the cost of healthcare," he said. "Something is out of balance."

Whelan now acts as an advocate for patients, for research, and for legislative action. He also participates in a support group, and is a member of the American Society of Clinical Oncology (ASCO). He is currently working on ASCO's CancerLinQ. program. Whelan's research on the long-term effects of chemotherapeutic agents on bone marrow has been widely published. **EBO**

THE AMERICAN JOURNAL OF MANAGED CARE Evidence-Based Oncology
The fight of our lives: unmet need in lung cancer **http://bit.ly/1PgYQJD**

Precision Therapeutics Can Pave the Path to Curing Cancer

SURABHI DANGI-GARIMELLA, PHD

What are we paying for when we pay for cancer care, and how do we do so sustainably?" was the question Joseph Alvarnas, MD, asked the audience at the 4th annual meeting of Patient-Centered Oncology Care. Alvarnas is the director of value-based analytics at City of Hope, Duarte, California, and also serves as editor-in-chief of *Evidence-Based Oncology*.

The question is important, especially as we move towards higher cure rates, innovative technologies, and services—the reimbursement structure needs to be dynamic, he thinks, to accommodate today's rapid changes in medicine. Alvarnas believes that the development of targeted immunotherapy agents has had a profound impact on patient outcomes and has brought "cure" into the picture.

JOSEPH ALVARNAS, MD

Presenting data that painted an upbeat picture of cancer cure rates, he said, "As of January 2014, there were 14.5 million cancer survivors," adding that analysis of the Surveillance, Epidemiology, and End Results program registry, between 2005 and 2011, saw the highest level, ever, of cancer survivorship across various cancer types, much of which he attributes to our greater understanding of the disease through genomic and proteomic advances. However, for some patients with advanced, refractory cancers, a cure might only be in the distant future.

HEMATOLOGICAL MALIGNANCIES AND PRECISION MEDICINE

Alvarnas then dug deeper, and provided a historic perspective of the field's understanding of blood-based cancers. Using acute lymphoblastic leukemia (ALL) as an example, he said, "It's only by moving forward from an early paradigm to a much more mature one, based upon understanding of the biology of cancer, that we've moved on."

The discovery of mustard gas during World War I led to the development of alkylating agents as chemotherapy, and in combination with surgery and radiation therapy, the 3 modalities are still used in the clinic today, said Alvarnas. Explaining the importance of the discovery of the Philadelphia chromosome—which led to the development of the tyrosine kinase inhibitors (TKIs)—and the use of fluorescence in-situ hybridization or FISH technology to accurately detect low levels of residual disease, Alvarnas said that the 2 developments, together, have resulted in complete hematological and molecular remissions. He believes TKIs "turned this disease into a chronic illness like diabetes, rather than to something that we would normally think as being an imminently devastating disease."

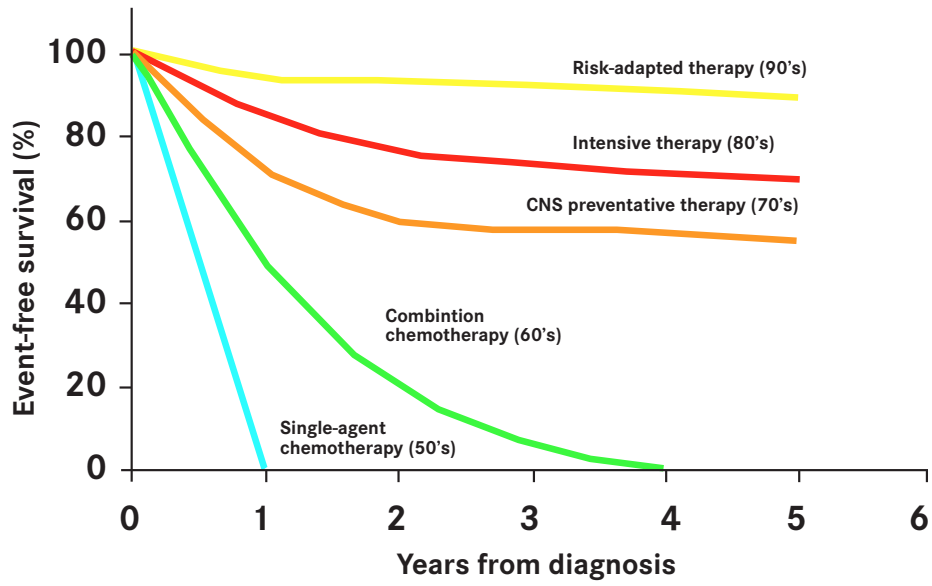
Precision medicine has radically altered the treatment landscape, according to Alvarnas; whether it be precision in diagnosis, guided by molecular diagnostic tests, or precision in treatment, with the various targeted therapeutics. The next step, he said, is "to fully leverage the information in therapeutic decision making."

"So these advances lead to more effective risk stratification and as we move towards discussions of payment, I don't think you could have a meaningful discussion of payment unless you include risk," said Alvarnas. He then went on to describe the disconnect that emerges with the International Classification of Diseases, or ICD codes, falling way short of being able to capture the nuances of the various therapeutic classes.

> **"For much of the duration of the war on cancer, we were unable to ask the right questions. We're now poised, through advances in technology, to ask the right scientific questions that, in fact, can translate through research to the cures that can really change this equation for patients broadly."**
>
> —JOSEPH ALVARNAS, MD, DIRECTOR, VALUE-BASED ANALYTICS, CITY OF HOPE

Alvarnas then shared a variety of genomic cluster maps of ALL patients of different age groups. "This gives you a sense of how chromosomes inform risk, and subsequently risk informs therapeutics," he said. Genome arrays, he explained, can provide significantly more detailed information on the genetic and genomic differences between different cancers, than would a microscopic slide with a tissue section. "Each one of these should be treated in a way that respects the molecular biology. These are the insights that are leading towards cancer cures."

What Is the Cumulative Effect of Improved Cancer Care Strategies in Pediatric ALL?



ALL indicates acute lymphoblastic leukemia.

Source: Joseph Alvarnas, MD, presented at Patient-Centered Diabetes Care 2015.

"So, the profound evolution in the therapeutic approach is that surgery, chemotherapy, and radiation therapy have in many ways been supplanted, and often replaced, by biological and targeted therapeutic technologies," including the TKIs, such as Bruton's tyrosine kinase inhibitors for chronic lymphocytic leukemia and non-Hodgkin lymphoma, immunomodulatory drugs or IMiDs and proteasomal inhibitors for myeloma and non-Hodgkin lymphoma, and ruxolitinib for myeloproliferative disorders.

THE NEXT FRONTIER: IMMUNOTHERAPEUTICS

"Harnessing the power of the immune system is becoming increasingly powerful in terms of its role in investigation and also translating into real therapeutics," Alvaranas explained, adding that nonoverlapping toxicities with traditional chemotherapy, the ability to specifically target tumor cells, and the lasting memory of the immune system are all significant advantages of this new direction in cancer care.

The armamentarium of immune-based therapies include monoclonal antibodies, monoclonal antibody–drug conjugates, and T-cell based therapeutics, such as the chimeric antigen receptor T cells, or CAR-T cells.

Narrating the profound influence of immunotherapy on patients with ALL, Alvarnas explained that, blinatumomab (used to treat ALL patients who express the CD19 receptor), helps bridge a patient—who would otherwise have died of his disease—to undergo transplant and subsequent cure. "And, again, the complete responses are quite extraordinarily high with 80% of patients treated with this agent achieving a molecular complete response." He also projected that CAR-T cells, which are currently being evaluated in phase 2 trials, would be an important addition to the cancer armamentarium.

"I think for the first time we have the tools necessary to find cures for many of our patients. For much of the duration of the war on cancer, we were unable to ask the right questions. We're now poised, through advances in technology, to ask the right scientific questions that, in fact, can translate through research to the cures that can really change this equation for patients broadly," said Alvarnas.

"For all of us who have had those uncomfortable discussions with patients in that we've not been able to offer meaningful therapy, we're having those conversations less frequently. I think we're better able to inform our conversations with a biological understanding, sometimes on a molecular level, of the diseases we treat and better match our patients to the therapeutic armamentarium that's available. And I look upon this with extraordinary hope," he concluded. **EBO**

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

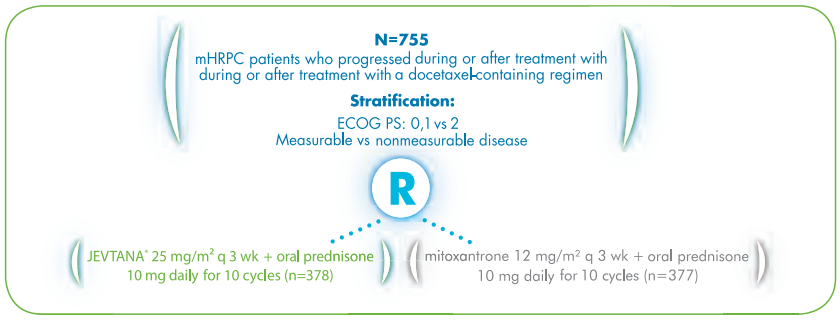
Please see additional Important Safety Information and Brief Summary of Full Prescribing Information, including boxed WARNING, on adjacent pages.

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: Overall Survival (OS)
- Secondary endpoints: Investigator-assessed tumor response,* safety, pharmacokinetics

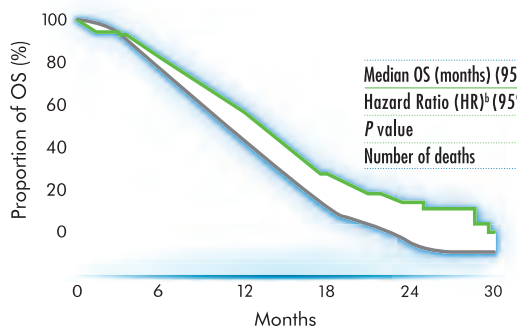
*For measurable disease according to RECIST criteria. RECIST=Response Evaluation Criteria In Solid Tumors.

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 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.

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[3]
- 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 WARNING, 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; June 2015. **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® is contraindicated in 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® is contraindicated in patients who have a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80.**

CONTRAINDICATIONS

- JEVTANA® is contraindicated in patients with:
  - neutrophil counts of ≤1,500/mm^3
  - history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80
  - severe hepatic impairment (total bilirubin > 3 x Upper Limit of Normal (ULN))

WARNINGS AND PRECAUTIONS

- Bone marrow suppression manifested as neutropenia, anemia, thrombocytopenia and/or pancytopenia may occur. 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
  - Caution is recommended in patients with hemoglobin < 10 g/dl
- Severe hypersensitivity reactions can occur.
  - Premedicate all patients with antihistamines, corticosteroids and H_2 antagonists prior to the initiation of the JEVTANA® infusion
  - Observe patients closely for hypersensitivity reactions, especially during the first and second infusions
  - Discontinue infusion immediately if severe 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:
  - JEVTANA® is contraindicated in patients with severe hepatic impairment (total bilirubin > 3 x ULN)
  - Dose should be reduced for patients with mild (total bilirubin > 1 to ≤ 1.5 x ULN or AST > 1.5 x ULN) and moderate (total bilirubin > 1.5 to ≤ 3.0 x ULN and any AST) hepatic impairment, based on tolerability data in these patients
  - Administer JEVTANA® with caution in patients with mild and moderate hepatic impairment and closely monitor for safety
- JEVTANA® can cause fetal harm when administered to a pregnant woman.
  - JEVTANA is not indicated for use in female patients
  - There are no adequate and well-controlled studies in pregnant women using JEVTANA®
  - Females 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 WARNING, on adjacent pages.

SANOFI ONCOLOGY

JEVTANA® (cabazitaxel) injection

JEVTANA® **Rx Only**
(cabazitaxel) injection, for intravenous use

Brief Summary of Prescribing Information

WARNING: NEUTROPENIA AND HYPERSENSITIVITY

Neutropenia: 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 is contraindicated in patients with neutrophil counts of ≤1,500 cells/mm^3 *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Severe hypersensitivity: 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 is contraindicated in patients who have a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80 *[see Dosage and Administration (2.1), Contraindications (4), and Warnings and Precautions (5.2)]*.

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 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.

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 *[see Warnings and Precautions (5.2)]*:

- 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 *[see Warnings and Precautions 5.3)]*.

JEVTANA injection single-use vial requires **two** dilutions prior to administration *[see Dosage and Administration (2.5)]*.

2.2 Dose Modifications for Adverse Reactions

Reduce or discontinue JEVTANA dosing for adverse reactions as described in Table 1.

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 granulocyte-colony stimulating factor (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 the 20 mg/m^2 dosage.

2.3 Dose Modifications for Hepatic Impairment

- Mild hepatic impairment (total bilirubin > 1 to ≤ 1.5 x Upper Limit of Normal (ULN) or AST >1.5 x ULN): Reduce JEVTANA starting dose to 20 mg/m^2.
- Moderate hepatic impairment (total bilirubin > 1.5 to ≤ 3 x ULN and AST = any): Reduce JEVTANA starting dose to 15 mg/m^2 based on tolerability data in these patients; however, the efficacy of this dose is unknown.
- Severe hepatic impairment (total bilirubin > 3 x ULN): Cabazitaxel is contraindicated in patients with severe hepatic impairment *[see Warning and Precautions (5.6) and Clinical Pharmacology (12.3) in the full prescribing information]*.

2.4 Dose Modifications for Use with 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]*.

2.5 Preparation and Administration

JEVTANA is a cytotoxic anticancer drug. Follow applicable special handling and disposable procedures *[see References (15) in the full prescribing information]*.[1] If JEVTANA first diluted solution, or second (final) dilution for intravenous infusion should come into contact with the skin or mucous, immediately and thoroughly wash with soap and water.

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

JEVTANA should not be mixed with any other drugs.

Preparation

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

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.

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.

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

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

Fully prepared JEVTANA 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 for a total of 24 hours (including the one-hour infusion) under the refrigerated conditions.

Discard any unused portion.

Administration

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.

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 administered intravenously as a one-hour infusion at room temperature.

4 CONTRAINDICATIONS

JEVTANA is contraindicated in patients with:

- neutrophil counts of ≤ 1,500/mm^3 *[see Warnings and Precautions (5.1)]*
- history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80 *[see Warnings and Precautions (5.2)]*
- severe hepatic impairment (total bilirubin > 3 x ULN) *[see Warnings and Precautions (5.6)]*

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

Bone marrow suppression manifested as neutropenia, anemia, thrombocytopenia and/or pancytopenia may occur. Neutropenic deaths have been reported. In the randomized trial, five patients (1.3%) 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. Grade 3–4 neutropenia has been observed in 82% of patients treated with JEVTANA in the randomized trial.

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 is contraindicated in patients with neutrophils ≤ 1,500/mm^3 *[see Contraindications (4)]*.

Caution is recommended in patients with hemoglobin < 10 g/dl.

5.2 Hypersensitivity Reactions

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.

Premedicate all patients prior to the initiation of the infusion of JEVTANA *[see Dosage and Administration (2.1)]*. Observe patients closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions require immediate discontinuation of the JEVTANA infusion and appropriate therapy. JEVTANA is contraindicated in patients with a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80 *[see Contraindications (4)]*.

5.3 Gastrointestinal Adverse Reactions

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. Antiemetic prophylaxis is recommended. Treat patients 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

In the randomized clinical trial, renal failure of any grade occurred in 4% of the patients being treated with JEVTANA, including four cases with fatal outcome. 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 Use in 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 Use in Patients with Hepatic Impairment

Cabazitaxel is extensively metabolized in the liver.

JEVTANA is contraindicated in patients with severe hepatic impairment (total bilirubin > 3 x ULN) *[see Contraindications (4)]*. Dose should be reduced for patients with mild (total bilirubin > 1 to ≤ 1.5 x ULN or AST > 1.5 x ULN) and moderate (total bilirubin > 1.5 to ≤ 3.0 x ULN and any AST) hepatic impairment, based on tolerability data in these patients *[see Dosage and Administration (2.3) and Use in Specific Populations (8.7)]*. Administration of cabazitaxel to patients with mild and moderate hepatic impairment should be undertaken with caution and close monitoring of safety.

5.7 Embryo-Fetal Toxicity

JEVTANA is not indicated for use in female patients.

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. Females 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:

- Bone Marrow Suppression *[see Warnings and Precautions (5.1)]*.
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*.
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.3)]*.
- Renal Failure *[see Warnings and Precautions (5.4)]*.
- Use in Elderly Patients *[see Warnings and Precautions (5.5)]*.
- Use in Patients with Hepatic Impairment *[see Warnings and Precautions (5.6)]*.
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.7)]*.

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
Skin and Subcutaneous Tissue Disorders				
Alopecia	37 (10%)	0	18 (5%)	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 (%)
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 CYP3A 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 (2.4) 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 is not indicated for use in female patients.

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

JEVTANA is not indicated for use in female patients.

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

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 death due to causes other than disease progression within 30 days of the last cabazitaxel dose were higher in patients who were 65 years of age or greater compared to younger patients *[see Warnings and Precautions (5.5)]*. The incidence of grade 3–4 neutropenia and febrile neutropenia were higher in patients who were 65 years of age or greater compared to younger patients. 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)]*.

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).

8.6 Renal Impairment

No dose adjustment is necessary in patients with renal impairment not requiring hemodialysis. Patients presenting with end-stage renal disease (creatinine clearance CL_{CR} < 15mL/min/1.73m^2), should be monitored carefully during treatment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

8.7 Hepatic Impairment

Cabazitaxel is extensively metabolized in the liver. Patients with mild hepatic impairment (total bilirubin > 1 to ≤ 1.5 x ULN or AST > 1.5 x ULN) should have JEVTANA dose reduced to 20 mg/m^2. Administration of cabazitaxel to patients with mild hepatic impairment should be undertaken with caution and close monitoring of safety *[see Clinical Pharmacology (12.3) in the full prescribing information]*. The maximum tolerated dose in patients with moderate hepatic impairment (total bilirubin > 1.5 to ≤ 3.0 x ULN and AST = any) was 15 mg/m^2, however, the efficacy at this dose level was unknown. Jevtana is contraindicated in patients with severe hepatic impairment (total bilirubin > 3x ULN) *[see Contraindications (4)]*.

10 OVERDOSAGE

There is no known antidote for JEVTANA overdose. Overdose has resulted from improper preparation *[see Dosage and Administration (2.5)]*. 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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As "Me-Too" Options Expand, Cost, Side Effects Become Considerations, McCullough Explains

ANDREW SMITH

The proliferation of new cancer treatments has created a novel challenge for oncologists and hematologists in recent years, said Stacey McCullough, PharmD, the senior vice president for pharmacy at Tennessee Oncology. For the first time, they frequently must decide which of several essentially similar medications makes the most sense for a particular patient.

Comparisons can be difficult, McCullough explained during the 4th annual meeting of Patient-Centered Oncology Care, which took place November 19-20, 2015. However, careful consideration of factors such as safety, adherence, and cost can help drive good decisions. To illustrate the growth of me-too cancer medications, McCullough highlighted drug approvals that occurred between 2009 and 2013. Those years produced 51 new drugs, 24 of which featured novel mechanisms for attacking tumors. And, if anything, the trend is accelerating.

"We could look to the last few weeks, and 6 or 7 new drugs, I think, have been approved," McCullough said. The most important criterion for choosing between similar drugs is efficacy, but it's generally impossible to discern the most effective product in a given class. Head-to-head trials are rare, while comparing results from one trial to another is nearly impossible. Different trials of different medications don't even share the same endpoint.

"If we look at the cohort of these drugs that were approved over the last 5 years, the endpoints were equally distributed," McCullough said. "Progression free survival, overall survival, or overall response rates were all equal endpoints of these studies."

The dearth of comparative evidence necessarily leads to broad guidelines. The National Comprehensive Cancer Network lists 3 tyrosine kinase inhibitors as first-line treatment options for chronic myelogenous leukemia (CML) and 17 sequence options (that use only 5 medications) for patients who eventually need 3 lines of therapy.

There are, however, strategies for caregivers who wish to use available information to establish preferences among apparently similar medications. For example, it is sometimes possible to compare safety and side-effect profiles and use those comparisons to decide which patients should get which medications. "Each of these molecules has distinctions that make them a little bit different," she said. "They exhibit different side-effect profiles, so they can be tailored to individual patients based on their comorbid position."

Choosing the medication that produces fewer side effects for the patient might actually increase its efficacy by increasing patient adherence to prescribed regimens. Choosing a medication that's used on an easy-to-remember schedule could do the same, although McCullough believes caregivers must also give patients better counseling in order to raise adherence rates.

"Go through their daily activities with them," she said. "Help them figure out when is the time that they can remember to take something once or twice a day. How do they need to take it in relationship to food? What about the other medications that they're taking? How do they need to store it? It's education on this level that's going to make a difference for the outcome."

McCullough also believes that cost comparisons can help caregivers make wise choices among otherwise similar medications. She noted that the total cost of the different CML medications can vary by $10,000 a month or $120,000 per year per patient. Multiply that by the 6000 new patients who will be diagnosed with the disease in any given year and systemic savings from consistently choosing the cheaper medication over the expensive alternative could reach $720 million.

McCullough urged caregivers to consider cost from the viewpoint of patient co-pays, as well. Co-pays can differ substantially among the various oral options, and there can also be substantial differences between any oral option and an intravenous treatment that's given in the office. "The last factor, and certainly not the least important when we talk about these oral medications, is that they do have the patient incur a higher co-pay in many instances," she said before warning about the dangers of prescribing oral medications that patients struggle to afford.

"Do they make concessions, split their doses, skip doses so that they can afford the next pill or so that the medication lasts a little bit longer?" McCullough asked. When the calendar turns to a new year, so can benefits, and providers should be mindful of this. "We can never take for granted that what a patient could afford yesterday is still affordable for them as we go forward." **EBO**

Are PBMs the Answer to Managing the High Cost in Oncology Care?

SURABHI DANGI-GARIMELLA, PHD

A pharmacist who engages in formulary decisions, a medical director for population management for a private health exchange, and an innovations leader at a pharmacy benefit manager (PBM), took to the podium at the 4th annual meeting of Patient-Centered Oncology Care, in Baltimore, Maryland, hosted by The American Journal of Managed Care, to discuss cost-saving strategies in oncology and the possibility of benefit managers playing a role in reining-in some of these costs.

"How do we assign value, and who will be responsible for the management? We need a new sheriff in town and maybe that will be the PBM," said Bruce A. Feinberg, DO, vice president of Clinical Affairs and chief medical officer at Cardinal Health.

Glen D. Stettin, MD, senior vice president of Clinical, Research, and New Solutions at Express Scripts said, "At Express Scripts, our customers are mainly tax payers, employers, self-insured patients, and the definition for value varies. Value for some is about access to care and for some it's about avoiding catastrophe. So we try to help our customers understand the dynamics and how to afford the benefit for everyone and to continue to deliver care for those who really need it."

Stettin continued that there's a big price differential when comparing drug prices in the United States with that in other western countries; drug prices are much lower in Europe, for instance, than here, and the government makes pricing decisions, vastly different from what we have here. "While I don't advocate the government to negotiate prices, the private sector needs to fill in this role," Stettin added.

"How do we assign value, and who will be responsible for the management?" asked panel moderator Bruce Feinberg, DO.

What can be the role of employers in this process?

Bruce W. Sherman, MD, FCCP, FACOEM, faculty at Case Western Reserve University School of Medicine, and medical director of Population Health Management Exchange Solutions, Buck Consultants at Xerox, pointed out that a

Bo Gamble, director, Strategic Practice Initiatives of the Community Oncology Alliance, in discussion with a fellow attendee.

quarter of individuals find their healthcare affordable, and these are people with private insurance. "So when we bring it down to the individual levels, it has become such a huge problem for individuals and the employers they work for: it's a crisis that makes them choose between treatment and going bankrupt," he said.

"From that perspective, employers really do not have the level of input from the individual's perspective to influence health plan or PBM perspectives, Sherman said. Advocacy groups could be in a better position to do that. Employers are relying on PBMs to be the hired gun to provide the level of control for healthcare service delivery so costs are not excessive for benefit enrollees.

Stacey W. McCullough, PharmD, senior vice president, Pharmacy, Tennessee Oncology, explained, "Physicians don't have it in their make-up to have financial conversations with their patient. It's hard to talk to the patient about that extra week of therapy when they really want to attend that wedding." These kind of choices that a patient may have to make are difficult for an oncologist to discuss with the patient.

McCullough explained that the preauthorization (PA) process and the number of FTEs that they have to maintain, indicate that access to care continues to grow. "We have 3 divisions within the clinic side; someone gets the PA and it rolls to foundation assistance or copay assistance. The administrative burden here is quite high. Also, with patent expirations, non-branded generics may not come with a big price difference compared with the branded product." However, co-pay assistance could be a problem for generics, she said. "This little offset can significantly increase patient cost."

Stettin defended the position that PBMs sometimes have to take. "Our job is to make drugs affordable. We did PA on 5 million of 1.3 billion prescriptions last year. Not approving therapy, sometimes folks do not follow evidence-based treatment; other times they are using experimental therapies—and we feel for the patient because they are desperate; but there are rules, and the intent of the health plan is to pay for therapy that is safe and effective. We have to enforce this policy, but it makes us unpopular," he said. The resulting savings can make treatment affordable for everyone, he said, offering the thousand-foot view of the current healthcare conundrum.

Sherman described the situation saying, "I think we are headed for a collision course between rapid growth of treatments and the society unwilling to pay for them. About 50% of US working adults earn less than $30,000 annually. With the incredible costs of available treatments, people have to make tough decisions on personal bankruptcy as an outcome of the need for treatment."

He wants physicians and care teams to consider this and wants to encourage patients, and their family members, to have frank conversations on cost of treatment with their treating physicians. "We'll be seeing more of this in the coming years," he added.

"I think there's that combustion in that while some steps of PA are definitely necessary, there may be an educational factor somewhere," said McCullough. "While physicians know something is expensive, they may not know the exact distinction. We have not tried to bog them down with the details. EMR [electronic medical record] and pathways that include a protocol analyzer may be something physicians may benefit from and might even want to know." In her opinion, the current situation might be the result of unintentional use of the more expensive drug by a physician, being blind to the cost differential.

"There are no ready answers here; there are ways to mitigate this by approaching these new treatments by aligning. There are no easy answers, however. Currently, we have science and technology growing at a much faster rate than wages and, consequently, the affordability gap is rapidly growing," Sherman said.

Stettin concluded that from a patient-centric standpoint, we need to think of what people will do. "Ask them, what is fair value for the drugs? We need affordable benefits for everyone. While I don't see PA going away, there will be transformation in terms of instant decision rendition, primarily for pharmacy benefit; we are getting there with medical benefit. While none of us like it, it saves a lot of money. We are working on a rationale for the best way to communicate the information," Stettin said. **EBO**

INNOVATIONS IN CARE

Putting Big Data to Work for Better Care in Oncology

MARY CAFFREY

Only 3% to 4% of all cancer patients take part in clinical trials, which means that the rest not only miss the possibility of new therapies, but also the chance for their data to become part of the collective record so that future patients may benefit from their experience.

ROBERT GREEN, MD

Flatiron Health, located in New York City, has been trying to change this since 2012. Robert Green, MD, a former community oncologist who is Flatiron's vice president for clinical strategy and senior medical director, said that without a clinical trial, "we essentially lose the patient experience; the voice of the patient, what they went through becomes lost."

Green, speaking at the 4th annual meeting of Patient-Centered Oncology Care, said too much oncology data is siloed; Flatiron's goal is to take the patient experience and make it into meaningful data. The company employs oncologists, quantitative scientists, and other medical information specialists to ensure the accuracy of the data being used to direct patient care. The company coined the term "technology-enabled abstraction," which refers to combining technology with qualified personnel who can pull information from pathology reports and other data sources.

"It's about trying to figure out how do you put all of the data points together so that in a structured and computerized way, you can look at a patient's experience over time using unstructured data from the EHR [electronic health record], structured data from the EHR, but also pulling together multiple external data sources," Green said.

Ultimately, Flatiron's technology helps oncologists identify candidates for diagnostic tests that might otherwise have been missed. Better use of technology also records important data such as dates of death, which may often be missed. Beyond the individual level, their technology also looks at how often certain tests are being ordered, in what type of patient, and when.

Data collected from practices can be used to look at individual patients without having to pay someone to look back into charts, Green said, in a way that "doesn't create a burden on [clinicians], but that allows them to get insight into how they're taking care of patients," and, hopefully, making improvements. He said this allows practices to ask, for example, "What is our lung cancer survival rate? How do (our rates) compare internally, and how do we look compared to other institutions, other practices, and other regions of the country?"

Besides looking back at data to see how practices can improve, community practices can use data to evaluate new patients and identify which ones might be candidates for a clinical trial. This will help raise the trial participation above 4%. "We need to increase that number, realizing that we're never going to be in an era where all patients go on what we consider now as standard prospective clinical trials," Green said. At the same time, getting data back to clinicians and researchers offers opportunities for all to learn "and hopefully improve care for all patients." **EBO**

In Previously Treated Metastatic NSCLC:

Change Expectations, Start With

OPDIVO™ (nivolumab)

INJECTION FOR INTRAVENOUS USE 10 mg/mL

INDICATION

OPDIVO® (nivolumab) is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.

SELECT IMPORTANT SAFETY INFORMATION

OPDIVO is associated with immune-mediated: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, rash, encephalitis, other adverse reactions; infusion reactions; and embryofetal toxicity.

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

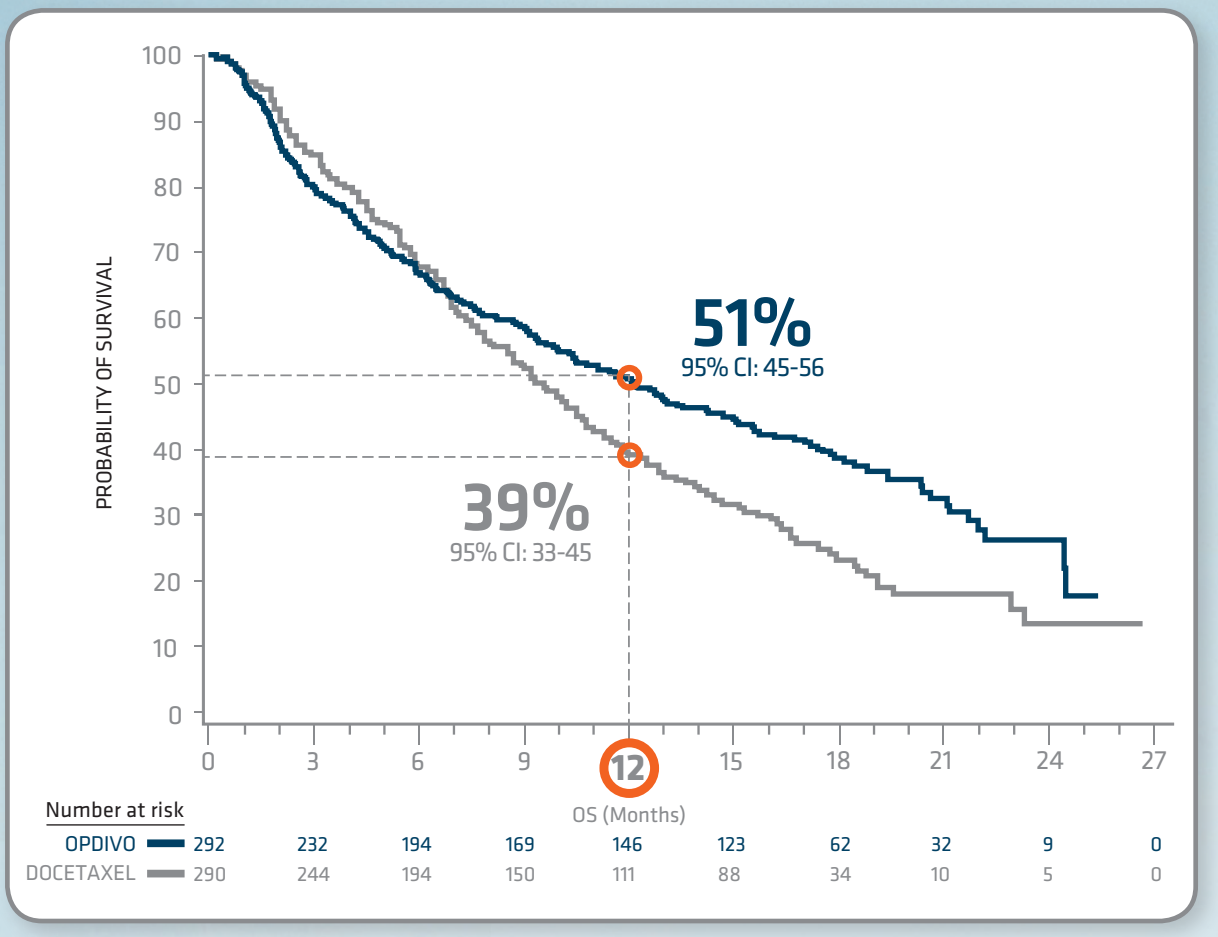
Please see additional Important Safety Information on the following page.

For Previously Treated Metastatic NSCLC Regardless of PD-L1 Expression

OPDIVO is the First and Only PD-1 Inhibitor Approved

NON-SQUAMOUS: Overall Survival[1,2]

Half of Patients Were Alive at 1 Year[2]



Refer to Figure 2 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.

Median OS was 12.2 months with OPDIVO (95% CI: 9.7-15.0) vs 9.4 months with docetaxel (95% CI: 8.0-10.7); HR=0.73 (95% CI: 0.60-0.89); *P*=0.0015.[1]

Objective response rate with OPDIVO was 19% (56/292; 4 complete responses, 52 partial responses) [95% CI: 15-24] vs 12% (36/290; 1 complete response, 35 partial responses) with docetaxel [95% CI: 9-17] (*P*=0.02). The median duration of response was 17 months in the OPDIVO arm and 6 months in the docetaxel arm.[1]

Median progression-free survival with OPDIVO was 2.3 months vs 4.2 months with docetaxel; HR=0.92 (95% CI: 0.77–1.11; *P*=0.39).[1]

Results were based on the prespecified interim analysis conducted when 413 events (93% of the planned number of events for final analysis) were observed (190 in the OPDIVO arm and 223 in the docetaxel arm).[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=292) vs docetaxel 75 mg/m^2 IV every 3 weeks (n=290) in patients with metastatic non-squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Appropriate prior targeted therapy may have been given to patients with known EGFR mutation or ALK translocation. The primary endpoint of the study was OS. Secondary endpoints included ORR and PFS.[1,2]

Serious Adverse Reactions

- In Checkmate 057, serious adverse reactions occurred in 47% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia, pulmonary embolism, dyspnea, pleural effusion, and respiratory failure.

Common Adverse Reactions

- In Checkmate 057, the most common adverse reactions (≥20%) reported with OPDIVO were fatigue (49%), musculoskeletal pain (36%), cough (30%), decreased appetite (29%), and constipation (23%).

ADDITIONAL IMPORTANT SAFETY INFORMATION

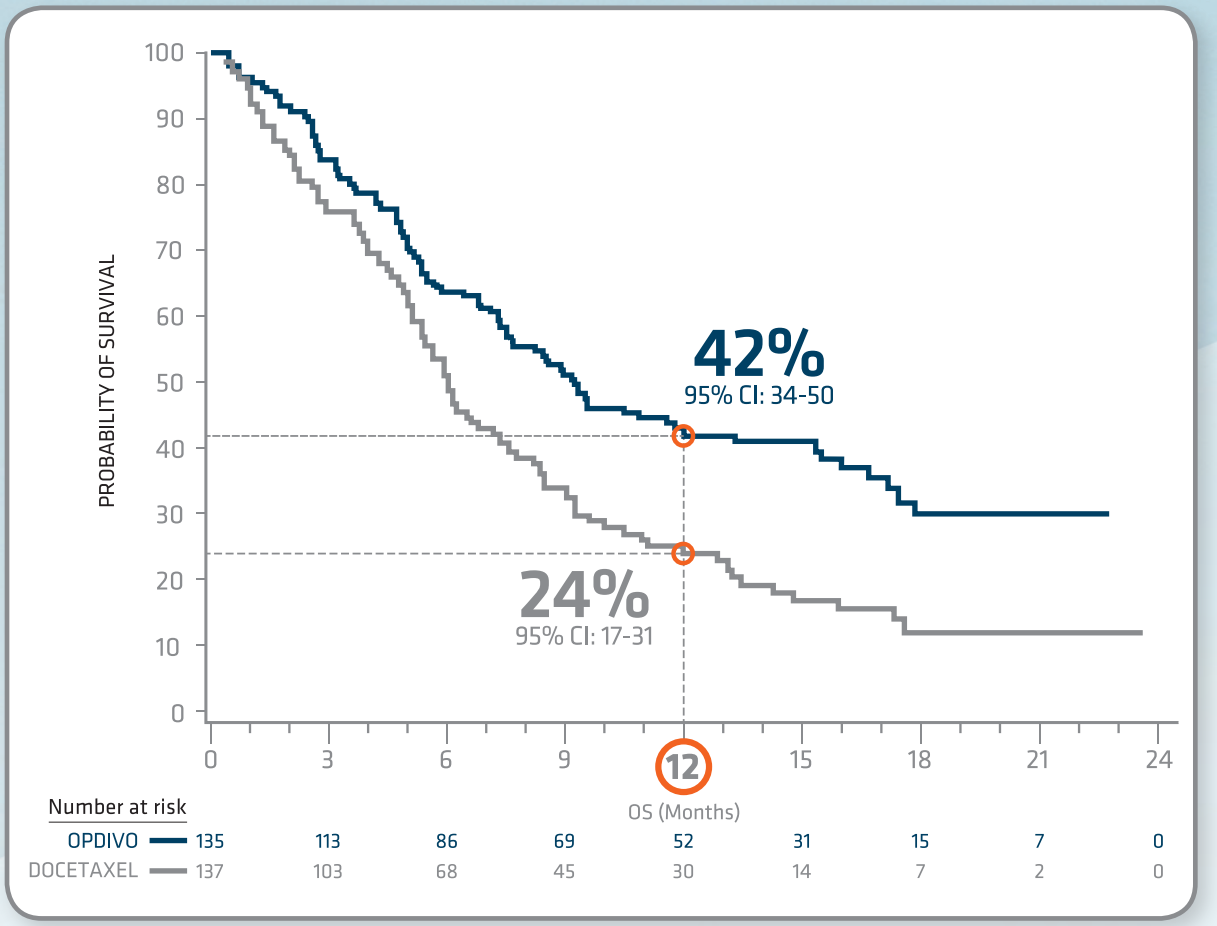
Immune-Mediated Pneumonitis

- Immune-mediated pneumonitis or interstitial lung disease, including fatal cases, occurred with OPDIVO treatment. Across the clinical trial experience with solid tumors, fatal immune-mediated pneumonitis occurred in 0.5% (5/978) of patients receiving OPDIVO as a single agent. In Checkmate 057, immune-mediated pneumonitis, including interstitial lung disease, occurred in 3.4% (10/287) of patients receiving OPDIVO including five Grade 3, two Grade 2, and three Grade 1 cases. Monitor patients for signs with radiographic imaging and symptoms of pneumonitis. Administer corticosteroids for Grade 2 or greater pneumonitis. Permanently discontinue OPDIVO for Grade 3 or 4 and withhold until resolution for Grade 2.

Based on Superior Overall Survival vs Chemotherapy*[1]

SQUAMOUS: Overall Survival[1,3]

The First and Only PD-1 Inhibitor to Nearly Double 1-Year Overall Survival Rate vs Chemotherapy*[1,3]



Refer to Figure 1 in the Full Prescribing Information for data on censored patients.
PD-L1=programmed death ligand 1.

Median OS was 9.2 months with OPDIVO (95% CI: 7.3-13.3) vs 6.0 months with docetaxel (95% CI: 5.1-7.3); HR=0.59 (95% CI: 0.44-0.79); *P*=0.00025.[1]

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]

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) in patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. The primary endpoint of the study was OS.[1,3]

*Docetaxel.

Start Now: The Only FDA Approved PD-1 Inhibitor That Does Not Require PD-L1 Testing.[1]

ADDITIONAL IMPORTANT SAFETY INFORMATION (cont'd)

Immune-Mediated Colitis

- Immune-mediated colitis can occur with OPDIVO treatment. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon restarting OPDIVO. In Checkmate 057, diarrhea or colitis occurred in 17% (50/287) of patients receiving OPDIVO. Immune-mediated colitis occurred in 2.4% (7/287) of patients including three Grade 3, two Grade 2, and two Grade 1 cases.

Please see additional Important Safety Information on the following page.

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

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 (cont'd)

Immune-Mediated Hepatitis

- Immune-mediated hepatitis can occur with OPDIVO treatment. 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 for Grade 3 or 4 immune-mediated hepatitis. In Checkmate 057, one patient (0.3%) developed immune-mediated hepatitis.

Immune-Mediated Endocrinopathies

- Hypophysitis, adrenal insufficiency, and thyroid disorders can occur with OPDIVO treatment. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency during and after treatment, and thyroid function prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater hypophysitis. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis. Administer corticosteroids for Grade 3 or 4 adrenal insufficiency. Withhold OPDIVO for Grade 2 and permanently discontinue for Grade 3 or 4 adrenal insufficiency. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. Adrenal insufficiency occurred in 1% (n=555) of patients receiving OPDIVO as a single agent. In Checkmate 057, Grade 1 or 2 hypothyroidism, including thyroiditis, occurred in 7% (20/287) and elevated TSH occurred in 17% of patients receiving OPDIVO. Grade 1 or 2 hyperthyroidism occurred in 1.4% (4/287) of patients.

Immune-Mediated Nephritis and Renal Dysfunction

- Immune-mediated nephritis can occur with OPDIVO treatment. Monitor patients for elevated serum creatinine prior to and periodically during treatment. For Grade 2 or 3 increased serum creatinine, 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. In Checkmate 057, Grade 2 immune-mediated renal dysfunction occurred in 0.3% (1/287) of patients.

Immune-Mediated Rash

- Immune-mediated rash can occur with OPDIVO treatment. Monitor patients for rash. Administer corticosteroids for Grade 3 or 4 rash. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 rash. In Checkmate 057, immune-mediated rash occurred in 6% (17/287) of patients receiving OPDIVO including 4 Grade 3 cases.

Immune-Mediated Encephalitis

- Immune-mediated encephalitis can occur with OPDIVO treatment. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out other causes. If other etiologies are ruled out, administer corticosteroids and permanently discontinue OPDIVO for immune-mediated encephalitis. Across clinical trials of 8490 patients receiving OPDIVO as a single agent or in combination with ipilimumab, <1% of patients were identified as having encephalitis. In Checkmate 057, fatal limbic encephalitis occurred in one patient (0.3%) receiving OPDIVO.

Other Immune-Mediated Adverse Reactions

- Based on the severity of adverse reaction, permanently discontinue or withhold treatment, administer high-dose corticosteroids, and, if appropriate, initiate hormone replacement therapy. The following clinically significant immune-mediated adverse reactions occurred in <2% (n=555) of single-agent OPDIVO-treated patients: uveitis, pancreatitis, abducens nerve paresis, demyelination, polymyalgia rheumatica, and autoimmune neuropathy. Across clinical trials of OPDIVO as a single agent administered at doses 3 mg/kg and 10 mg/kg, additional clinically significant, immune-mediated adverse reactions were identified: facial nerve paralysis, motor dysfunction, vasculitis, diabetic ketoacidosis, and myasthenic syndrome.

Infusion Reactions

- Severe infusion reactions have been reported in <1% of patients in clinical trials of OPDIVO. In Checkmate 057, Grade 2 infusion reactions occurred in 1% (3/287) of patients receiving OPDIVO. Discontinue OPDIVO in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions.

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-containing regimen 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-containing regimen, advise women to discontinue breastfeeding during treatment.

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.** Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. *N Engl J Med*. doi:10.1056/NEJMoa1507643. **3.** Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. *N Engl J Med*. 2015;373(2): 123-135.

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

Bristol-Myers Squibb

Printed in USA. 1506US1502049-02-01 10/15

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 non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO *[see Clinical Studies (14.2) in full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Immune-Mediated Pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of corticosteroids and no clear alternate etiology, including fatal cases, occurred with OPDIVO treatment. Across clinical trial experience with solid tumors receiving OPDIVO as a single agent, fatal immune-mediated pneumonitis occurred in 0.5% (5/978) of patients. 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).

Monitor patients for signs with radiographic imaging and symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (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 (2.3) in full Prescribing Information]*.

In Trial 3, pneumonitis, including interstitial lung disease, occurred in 3.4% (10/287) of patients receiving OPDIVO. Of these 10 patients, there were five patients with Grade 3, two patients with Grade 2, and three patients with Grade 1 immune-mediated pneumonitis. The median time to onset was 7.2 months (range: 2.7 to 13.1 months). All five patients with Grade 3 and one of two patients with Grade 2 pneumonitis received high-dose corticosteroids and permanently discontinued OPDIVO; two of these seven were documented radiographically to have complete resolution of pneumonitis. One patient with Grade 2 pneumonitis had OPDIVO temporarily withheld, received low-dose corticosteroids, experienced complete resolution and was retreated without recurrence of pneumonitis.

Immune-Mediated Colitis

Immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology, can occur with OPDIVO treatment. Monitor patients for signs and symptoms of 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 moderate or severe (Grade 2 or 3) colitis. Permanently discontinue OPDIVO for life-threatening (Grade 4) or for recurrent colitis upon restarting OPDIVO *[see Dosage and Administration (2.3) in full Prescribing Information]*.

In Trial 3, diarrhea or colitis occurred in 17% (50/287) of patients receiving OPDIVO. Immune-mediated colitis occurred in 2.4% (7/287) of patients: three patients with Grade 3, two patients with Grade 2, and two patients with Grade 1. The median time to onset in these seven patients was 2.7 months (range: 4 weeks to 19 months). All seven patients received corticosteroids, six of these seven received high-dose corticosteroids for a median duration of 2.9 weeks (range: 1 week to 2.1 months). One patient with Grade 3 colitis permanently discontinued OPDIVO. All seven patients experienced complete resolution. Five of the seven patients were retreated after complete resolution without recurrence of diarrhea or colitis.

Immune-Mediated Hepatitis

Immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology, can occur with OPDIVO treatment. 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 moderate (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 (2.3) in full Prescribing Information and Adverse Reactions]*.

In Trial 3, one patient developed immune-mediated hepatitis (0.3%) after 7.8 months of OPDIVO exposure. The event resolved following temporary withholding of OPDIVO and high-dose corticosteroid therapy. Immune-mediated hepatitis recurred following resumption of OPDIVO, resulting in permanent discontinuation.

Immune-Mediated Endocrinopathies

Hypophysitis

Hypophysitis can occur with OPDIVO (nivolumab) treatment. Monitor patients for signs and symptoms of hypophysitis. Administer corticosteroids at a dose of 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or greater hypophysitis. Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3) and permanently discontinue OPDIVO for life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Adrenal Insufficiency

Adrenal insufficiency can occur with OPDIVO treatment. Monitor patients for signs and symptoms of adrenal insufficiency during and after treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency *[see Dosage and Administration (2.3) in full Prescribing Information]*.

In Trials 1 and 3 (n=555), 1% of OPDIVO-treated patients developed adrenal insufficiency.

Hypothyroidism and Hyperthyroidism

Thyroid disorders can occur with OPDIVO treatment. 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.

In Trial 3, Grade 1 or Grade 2 hypothyroidism, including thyroiditis, occurred in 7% (20/287) of patients receiving OPDIVO and 0% (0/268) of patients receiving docetaxel, while elevated TSH occurred in 17% of patients receiving OPDIVO and 5% of patients receiving docetaxel. The median time to onset of hypothyroidism/thyroiditis was 2.9 months (range: 1.4 to 11.8 months). All 20 patients received levothyroxine. Two patients received corticosteroids; one of whom received high-dose corticosteroids. Complete resolution of hypothyroidism occurred in one patient. OPDIVO was temporarily withheld due to hypothyroidism/thyroiditis in three patients; no patients discontinued OPDIVO due to hypothyroidism/thyroiditis.

Grade 1 or Grade 2 hyperthyroidism occurred in 1.4% (4/287) of patients. The median time to onset was 2 months (range: 4.1 weeks to 2.8 months). Two of four patients received methimazole and one patient also received treatment with high-dose corticosteroids. All four patients experienced complete resolution.

Immune-Mediated Nephritis and Renal Dysfunction

Immune-mediated nephritis, defined as renal dysfunction or ≥Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology, can occur with OPDIVO treatment. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, 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. Permanently discontinue OPDIVO and administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) increased serum creatinine *[see Dosage and Administration (2.3) in full Prescribing Information and Adverse Reactions]*.

In Trial 3, immune-mediated renal dysfunction (Grade 2) occurred in 0.3% (1/287) of patients. The time to onset in this patient was 1.5 months. The patient permanently discontinued OPDIVO, received high-dose corticosteroids, and experienced complete resolution.

Immune-Mediated Rash

Immune-mediated rash can occur with OPDIVO treatment. Monitor patients for rash. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for severe (Grade 3) or life-threatening (Grade 4) rash. Withhold OPDIVO for severe (Grade 3) rash and permanently discontinue OPDIVO for life-threatening (Grade 4) rash *[see Dosage and Administration (2.3) in full Prescribing Information]*.

In Trial 3, immune-mediated rash occurred in 6% (17/287) of patients receiving OPDIVO. Grade 3 rash developed in four patients (1.4%), of whom one discontinued treatment.

Immune-Mediated Encephalitis

Immune-mediated encephalitis can occur with OPDIVO treatment. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to serve neurologic deterioration. Evaluation may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for immune-mediated encephalitis *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Across clinical studies of 8490 patients receiving OPDIVO, less than 1% of patients were identified as having encephalitis. In Trial 3, fatal limbic encephalitis occurred in one patient (0.3%) receiving OPDIVO after 7.2 months of exposure. OPDIVO was discontinued; corticosteroids were administered.

Other Immune-Mediated Adverse Reactions

Other clinically significant immune-mediated adverse reactions can occur. Immune-mediated adverse reactions may occur after discontinuation of OPDIVO (nivolumab) therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or 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 (2.3) in full Prescribing Information]*.

The following clinically significant, immune-mediated adverse reactions occurred in less than 2% of OPDIVO-treated patients in Trials 1 and 3 (n=555): uveitis, pancreatitis, abducens nerve paresis, demyelination, polymyalgia rheumatica, and autoimmune neuropathy.

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: facial nerve paralysis, motor dysfunction, vasculitis, diabetic ketoacidosis, and myasthenic syndrome.

Infusion Reactions

Severe infusion reactions have been reported in <1% of patients in clinical trials of OPDIVO as a single agent. In Trial 3, Grade 2 infusion reactions occurred in 1% (3/287) of patients receiving OPDIVO. Discontinue OPDIVO in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions.

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 Endocrinopathies *[see Warnings and Precautions]*
- Immune-Mediated Nephritis and Renal Dysfunction *[see Warnings and Precautions]*
- Immune-Mediated Rash *[see Warnings and Precautions]*
- Immune-Mediated Encephalitis *[see Warnings and Precautions]*
- Other Immune-Mediated Adverse Reactions *[see Warnings and Precautions]*
- Infusion 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 practice.

The data in the Warning and Precautions section reflect exposure to OPDIVO for clinically significant adverse reactions in 978 patients enrolled in Trials 1, 3, a single-arm trial in NSCLC, or an additional dose finding study (n=306) administering OPDIVO as a single agent at doses of 0.1 to 10 mg/kg every 2 weeks *[see Warnings and Precautions]*.

The data described below reflect exposure to OPDIVO in Trial 3, which is a randomized trial in patients with metastatic non-squamous non-small cell lung cancer (NSCLC).

Metastatic Non-Squamous Non-Small Cell Lung Cancer

The safety of OPDIVO was evaluated in Trial 3, a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen *[see Clinical Studies (14.2) in full Prescribing Information]*. Patients received 3 mg/kg of OPDIVO (n=287) administered intravenously over 60 minutes every 2 weeks or docetaxel (n=268) administered intravenously at 75 mg/m^2 every 3 weeks. The median duration of therapy was 2.6 months (range: 0 to 24.0+) in OPDIVO-treated patients and was 2.3 months (range: 0 to 15.9 months) in docetaxel-treated patients. In this trial, 30% of patients received OPDIVO for greater than 6 months and 20% of patients received OPDIVO for greater than 1 year.

Trial 3 excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease.

The median age of all randomized patients was 62 years (range: 21 to 85); 37% of patients in the OPDIVO (nivolumab) group were ≥65 years of age and 47% of patients in the docetaxel group were ≥65 years of age, 55% were male, and 92% were white. Twelve percent of patients had brain metastases and ECOG performance status was 0 (31%) or 1 (69%).

OPDIVO was discontinued in 13% of patients, and was delayed in 29% of patients for an adverse reaction. Serious adverse reactions occurred in 47% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pleural effusion, and respiratory failure. In the OPDIVO arm, seven deaths were due to infection including one case of pneumocystis jirovecii pneumonia, four were due to pulmonary embolism, and one death was due to limbic encephalitis.

The most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, cough, decreased appetite, and constipation. Table 1 summarizes selected adverse reactions occurring more frequently in at least 10% of OPDIVO-treated patients.

Table 1: Selected Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (Trial 3)

Adverse Reaction	OPDIVO (n=287)		Docetaxel (n=268)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	Percentage (%) of Patients			
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	30	0.3	25	0
Metabolism and Nutrition Disorders				
Decreased appetite	29	1.7	22	1.5
Gastrointestinal Disorders				
Constipation	23	0.7	17	0.7
Skin and Subcutaneous Tissue Disorders				
Pruritus	11	0	1.9	0

Other clinically important adverse reactions observed in patients treated with OPDIVO and which occurred at a similar incidence in docetaxel-treated patients and not listed elsewhere in section 6 include: fatigue/asthenia (49% Grade 1-4, 6% Grade 3-4), musculoskeletal pain (36%), pleural effusion (5.6%), pulmonary embolism (4.2%), urticaria (1.4%), and polymyalgia rheumatica (0.3%).

Table 2: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of OPDIVO-Treated Patients for all NCI CTCAE Grades and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (Trial 3)

Test	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	OPDIVO		Docetaxel	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Chemistry				
Hyponatremia	35	6	32	2.7
Increased AST	28	2.8	14	0.4
Increased alkaline phosphatase	27	1.1	18	0.4
Increased ALT	23	2.4	15	0.4
Increased creatinine	18	0	13	0.4
Increased TSH[b]	17	N/A	5	N/A

[a]Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 280 to 287 patients) and docetaxel group (range: 252 to 262 patients); TSH: OPDIVO group n=209 and docetaxel group n=207.
[b]Not graded per NCI CTCAE v4.0.

Immunogenicity

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

Of 532 patients who were treated with OPDIVO (nivolumab) 3 mg/kg every 2 weeks and evaluable for the presence of anti-nivolumab antibodies, 67 patients (12.6%) tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay. Neutralizing antibodies against nivolumab were detected in five patients (0.9%). There was no evidence of altered pharmacokinetic profile or toxicity profile with anti-nivolumab binding antibody development.

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 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

Of the 292 patients randomized to OPDIVO in Trial 3, 37% of patients were 65 years or older and 7% were 75 years or older. In this trial, no overall differences in safety or efficacy were reported between elderly patients and younger patients.

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]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, and hyperthyroidism *[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]*.
- Rash: Advise patients to contact their healthcare provider immediately for rash *[see Warnings and Precautions]*.
- Encephalitis: Advise patients to contact their healthcare provider immediately for neurological signs or symptoms of encephalitis *[see Warnings and Precautions]*.
- Infusion Reactions: Advise patients of the potential risk of infusion reaction *[see Warnings and Precautions]*.
- Females of Reproductive Potential: 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]*.
- Lactation: Advise women not to breastfeed while taking OPDIVO *[see Use in Specific Populations]*.

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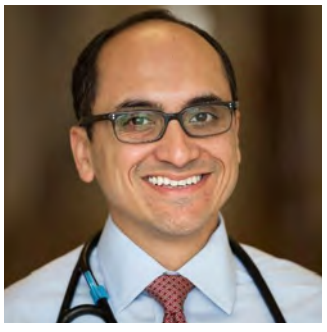
Bridging the Communication Gap to Overcome "Financial Toxicity"

MARY CAFFREY

Nearly 3 years ago, Duke University's Yousuf Zafar, MD, MHS, gave a name to the experience of a growing number of cancer patients—including those with insurance—when he and a coauthor coined the term "financial toxicity."[1]

In a pair of essays in the journal *Oncology*, they described the stress, cost burdens, and poor quality of life among patients whose out-of-pocket costs were soaring along with cost of the blockbuster drugs designed to treat their cancer. Most striking has been the phenomenon of nonadherence—patients who skip doses, cut pills in half, or abandon prescriptions at the counter—because they can't afford to pay.



YOUSUF ZAFAR, MD, MHS

What is an oncologist to do? Much has happened, in the meanwhile, to advance the conversation that Zafar helped start in 2013; and, at the 4th annual meeting of Patient-Centered Oncology Care, he presented results from a recent study in *The American Journal of Managed Care* (*AJMC*) on the gap between the conversations that cancer patients want to have with their doctors and what actually occurs.[2] While this might seem frustrating, Zafar and his colleagues find that when patients and oncologists connect on cost issues, the outcome is often positive without any compromises in care.

Zafar described the cost conversation as a process; for someone like him who studies the value of cancer therapies, there's the constant tug-of-war between the big picture and "the patient in front of me." Patients, too, evolve in their thinking. "Particularly the first time that patients meet me as an oncologist, they don't want cost on the list," of treatment considerations. "And the question is, at what point does it become part of the decisionmaking, and when does it become important?"

LITTLE RELATIONSHIP BETWEEN COST, BENEFIT

The discussion over the high cost of cancer drugs has brought out some interesting facts, Zafar said. A *JAMA Oncology* study found very little relationship between cost and improvement over the current standard of care among 51 cancer drugs. Despite what patients share with their doctors about the stress of paying for therapy, Zafar said, research shows the amazing steps patients will take to pay for care; 39% would be willing to sell their home.

The question for clinicians and policymakers, of course, is, what happens to patients who experience this level of distress?

Zafar reviewed a study presented at the meeting of the American Society of Clinical Oncology (ASCO), which compared cancer patients, who declared bankruptcy, with those who did not. "What they found is that in over 7000 matched patients, those who declared bankruptcy had a 79% greater mortality risk," he said.

Why does this happen? Zafar has studied this, and, among patients with insurance, there is a willingness to cancel vacations, cut back on groceries, or spend retirement savings. All this affects quality of life and well-being. "But I think the factor that is most important and best explains this relationship between financial distress and greater risk of mortality is quality of care. And, quality of care is defined by adherence."

He described a study involving imatinib (Gleevec), which found that within 6 months of starting the drug, patients with higher copays were 70% more likely to be nonadherent. More striking was that the threshold for the higher copay was $53 a month. Today, most copays for the oral agents Zafar prescribes are $80 a month. "This just goes to show how sensitive our patients and their budgets are to small changes as a result of cancer treatment."

Zafar reviewed the value calculators created by ASCO and the National Comprehensive Cancer Network, and the DrugAbacus created by Memorial Sloan Kettering Cancer Center. While they are helpful in some ways, "None of these really describe how much a patient is going to pay for any of these particular interventions," he said. Things change patient to patient, month to month, making predictions very difficult.

TALKING TO PATIENTS WORKS

Zafar led a study published in *AJMC*, in September 2015,[2] which found that 51% of cancer patients wanted to discuss cost considerations with their doctors, but only 19% actually do. The study, based on a survey of 300 patients taken between November 2012, and June 2013, found that the willingness to discuss cost increased as treatment progressed and the bills began to mount.

While comparatively few patients discussed their financial burdens, those who did got results. Fifty-seven percent said their costs were reduced, and 75% of these said this happened without any change to their treatment plan—meaning their doctor was able to press harder with the insurer or find the patient some financial assistance.

Why don't patients bring up their financial stress to their oncologist? Some think it's not the doctor's job, and some are simply embarrassed.

Zafar said oncologists must keep in mind that the value equation will differ for each patient, and it will change as the disease progresses. "There's cost and value to society. There's cost and value to the patient. The challenge is to figure out where we can find the overlap." **EBO**

Why haven't you talked about costs with your doctor?

I have no difficulties affording care	**(53%)**
I want the best possible care regardless of costs	**(34%)**
My doctor shouldn't have to worry about my finances/not my doctor's job	(23%)
My doctor doesn't know how to help or would not be able to help with my costs	**(19%)**
I have talked to someone else (like a social worker or counselor) about my costs of care	**(11%)**
I am embarrassed about discussing costs with my doctor	**(5%)**
Other	**(3%)**
Refused	**(<1%)**

Source: Zafar SY, Chino F, Ubel PA, et al. The utility of cost discussions between patients with cancer and oncologists. *Am J Manag Care*. 2015;21(9):607-615.

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1. Zafar SY, Abernethy AP. Financial toxicity, part I: a new name for a growing problem. *Oncology (Williston Park)*. 2013;27(2):80-81, 149.
2. Zafar SY, Chino F, Ubel PA, et al. The utility of cost discussions between patients with cancer and oncologists. *Am J Manag Care*. 2015;21(9):607-615.

Outdated Metrics in the Age of Precision Medicine

TONY HAGEN

With the rapid pace of change in precision medicine, insurance companies and federal policymakers will need to adjust for far more variance in the ways patients are treated, even though insurance plans and federal policy, by nature, require a measure of standardization, according to experts who took part in a panel discussion at the 4th annual meeting of Patient-Centered Oncology Care, presented in Baltimore, Maryland, by *The American Journal of Managed Care*.

Panelists were not fully convinced that payment and federal policies can make the evolutionary leap with grace, given that government measurement tools are sometimes inadequate, and many elements in oncologic care lack coordination and transparency.

"The challenge for us is how to deal with this infrastructure that's very outdated as we're using it today, yet we need to build the moonshot vehicle with these technologies, with these policies; and that's where I see a lot of room for creativity," said Kavita Patel, MD, a primary care internist at Johns Hopkins Medicine and a former director of policy for the Obama Administration.

The session entitled, "Navigating the Conflict of Personalized Medicine vs Population Management", covered a wealth of unresolved issues that pose challenges for today's physicians, policymakers, and payers as medical science races forward and creates a knowledge vacuum that requires all parties to act with more nimbleness, while shedding institutionalized methodology, which can inhibit the effective delivery of personalized care.

"When we think about personalized medicine, we become so fixated on molecular diagnostic studies that we forget

that we're thinking about a person, and to the extent that we connect all of this technology and honor the humanity of the person, the closer we get to doing the right thing," said Joseph Alvarnas, MD, director of value-based analytics at City of Hope National Medical Center in Duarte, California.

Finding the right marriage between delivering on value and paying the correct amount of attention to technology is still in the realm of a Holy Grail quest, he said. "For us, it's finding the right valuation tools to glean for our patients whether we're adequately serving their needs, and that's tough. I haven't seen a perfect tool yet."

Population health and precision medicine couldn't be more at odds with each other than cats and dogs, said Burton F. VanderLaan, MD, medical director at Priority Health, a nonprofit insurer in western Michigan. Population health looks at the whole cost of care, with a focus on chronic conditions and social determinants of health. The desire is to standardize treatment and to reduce variation through the use of guidelines, partly through coverage policy, VanderLaan said.

On the other hand, precision medicine in oncology puts the emphasis on allowing for broader variations in care because of the focus on highly individualized therapy, he said. There is no general goal to improve the health of the overall population. "This is the interesting paradigm that the health clinics are operating under," VanderLaan said. Payers, he said, are going to be challenged to "reinvestigate the evidentiary basis that they use to determine coverage policy." Science is outpacing the slow and steady progress of clinical trials, to the

point that "we just don't have the luxury of waiting for them in order to craft appropriate coverage policy," he said, adding that the solution being imposed upon payers is that they base their coverage decisions on varying levels of evidence, among them adaptive trials, phase 2 trials, and basket trials. "Plans will have to become a lot more comfortable with the notion of variation, because when you're individualizing therapy, that's going to become a given," he said.


KAVITA PATEL, MD

MEASURING THE QUALITY OF CARE

The tools needed for measuring the effectiveness of care in this new environment just don't measure up, said Alvarnas. He said that part of his job at City of Hope is "creating a language that's transparent enough to transcend the limitations of ICD-9 and ICD-10, so that you can spot good care when you see it and mismatches when they occur."

In an ideal world, a shift to value-based payments would be much more patient-centered than what exists right now, said Patel. "I don't think patients care so much if it's a fee-for-service setting, or a capitated setting, or an episodic/bundled setting. They just want to see those outcomes that they desire." Part of the problem is that physicians have to think in terms of population management, whereas patients may simply want more time in the examination room with their doctors. "That can create a tension," Patel said.

When the discussion shifted to financial health literacy, Patel argued that there isn't enough transparency in health costs to guide patient financial decisions. "When I worked in the administration, I wanted to inject more of a forced conversation about copayments, deductibles, premiums, and out-of-pocket costs," she said. "The rules and regulations tried to cover those issues. I don't think they have. Most physicians that I work with are not equipped to talk about the financing of healthcare with most patients, and most patients when they come to access the health system for the first time are actually kind of shocked by how little they know about their own payments and deductibles."

She cited an example of how "coverage" under a plan may actually mean an 80% out-of-pocket cost for a particular drug. "In the United States, it matters where you get care, and you can't even use experiences from one market to another to make assumptions," she said.

There's truth in that, but you may end up shortchanging the patient if you try to commoditize healthcare down (to) the penny the way other products and services are sold in the United States, Alvarnas said. "I would argue that then we lose the integrity of healthcaredelivery that allows us to take a very sick patient and hopefully have one who's restored to health at the end of it," he said.

VanderLaan said an "unstructured and siloed" healthcare system is partly to blame for the existence of information bulkheads that allow information to flow freely in some sectors and poorly in others. "In different communities there are very different levels of integration." **EBO**

ACCOUNTABLE CARE

Panelists Predict FFS Will Grow More Cumbersome

TONY HAGEN

Tremendous consolidation of remaining independent oncology practices is very likely under scenarios painted by panelists at the 4th annual meeting of Patient-Centered Oncology Care, presented by *The American Journal of Managed Care*.


TED OKON

The closing panel discussion of the 2-day event brought together an independent practice representative and a former director of medical policy development for the FDA. CMS has a strong desire to make accountable care organizations (ACOs) work, but there are many variables, and panelists said further experimentation with this form of care could have the effect of driving physicians out of fee-for-service (FFS) and into Medicare Advantage, where group health programs administer Medicare payment.

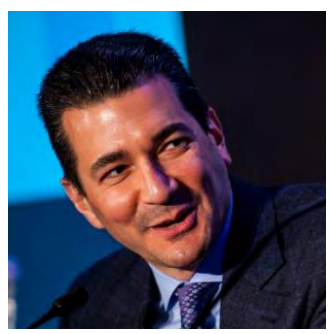
However, the degree to which oncology practices will participate in this migration is unclear because many of them are falling into the gravitational pull of expanding hospital systems, the panelists said. Yale-New Haven Hospital is an example of a growing, all-encompassing conglomerate, said participant Ted Okon, executive director of the Community Oncology Alliance (COA): "What's called Jaws in Connecticut is also known as Yale. They've bought up everything in the entire state."

CMS has attempted to tailor ACOs to a variety of health organizations so that each is comfortable with the level of risk it is undertaking though participation. The Medicare Access & CHIP Reauthorization Act, for example, offers the choice of participation in an alternative payment model or FFS. Similarly, the Oncology Care Model, scheduled for launch in spring of 2016, allows for innovative forms of reimbursement.

These programs have yet to show their worth, and there is evidence that ACOs have stumbled in various respects, other panelists responded. Okon said that ACOs reminded him of homeowners associations that require numerous permissions even for relatively minor things, such as paint colors and landscaping. Despite that level of control, a single large expense for an uncovered drug can take a practice completely by surprise and "bust the bank," Okon said.

On the other hand, he added, raising the example of the Oncology Medical Home form of integrated care that COA has promoted, better coordination and patient-centered care can enable a family to avoid a trip to the emergency department because off-hours oncology care is available through a practice location. In one such instance, payment was vastly simplified, Okon said. "It wasn't 'Ka-ching! Ka-ching! Ka-ching!'"

Another problem with the increasing emphasis on ACOs has to do with the government's lack of experience with managing multiple complex payment models and measuring outcomes, said panelist Scott Gottlieb, MD, a resident fellow at the American Enterprise Institute and a former medical policy development director at the FDA. "They're not necessarily having the outcomes that CMS had hoped for," he said, adding that the future for ACOs doesn't look promising. "I think they'll be hard-pressed to make these partially capitated models and the ACO construct work. You're seeing more rhetoric in Washington from individuals who were previously champions of ACOs who recognize some of the growing pains. Now they're saying, 'Well, they weren't the ultimate model we had in mind. They were there to test the transfer of risk,' so you're seeing some moving away. In a field that is as fast-moving as oncology, reimbursement models that are based on backward measures of risk and cost are going to make it more challenging in this setting than others."


SCOTT GOTTLIEB, MD

As these programs falter, CMS is likely to fall back on elements of cost management, with which it has been successful, such as bundled care, Gottlieb said. The panel also touched on measures of performance. Okon noted the recent efforts of a COA steering committee to develop a set of 18 quality and value measures, which the alliance has said some payers have begun to accept. It's not easy, though, to get more payers to accept these measures, he said. "We're trying to run with something that will actually work and is actually good patient medicine. The problem is that the system around us can't move fast enough."

Gottlieb, though, said he wasn't convinced that quality measures translate to successful innovation. "The problem in these policy constructs is that you never learn to run because you're so busy crawling. When you default to a certain set of measures, it becomes static and hard to change." **EBO**

Family Members Prefer Compassionate End-of-Life Care for Cancer Patients

SURABHI DANGI-GARIMELLA, PHD

A claims-based retrospective study in a Medicare population, published in *JAMA*, has found that family members of patients who died of cancer were more likely to report the patient's end-of-life (EOL) care as "excellent" if hospice care was longer than 3 days, if patients were not admitted to the intensive care unit (ICU) within the last 30 days of death, or if the patient died outside of a hospital setting.

The results of this study underscore the importance of advance care planning in improving the quality of care that patients receive at EOL, ensuring that the treatment or care the patient receives meets their goals of care.

The study included analysis of interviews with 1146 bereaved family members of Medicare patients with advanced lung or colorectal cancer who had died by 2011. The study examined claims-based quality measures of aggressive EOL care, which included ICU admission or repeat hospitalizations or emergency department visits during the last 30 days of life, chemotherapy administered in the last 2 weeks of life, no hospice of less than 3 days of hospice, and death in the hospital.

Of the 1146 patients, 51.3% family members reported EOL care as excellent. Additionally, about 59% of family members were happy if hospice care extended beyond 3 days, but 45% were unhappy if the patients was in the ICU 30 days prior to death. More than 42% of family members of patients who died in the hospital setting reported being unhappy with EOL care.

The authors concluded that earlier hospice enrollment, avoidance of ICU admissions within 30 days of death, and death occurring outside the hospital were associated with perceptions of better EOL care, and that their findings are supportive of advance care planning consistent with the preferences of patients.

"Interventions should focus more on increasing early hospice enrollment and decreasing ICU admissions and hospital deaths," lead study author Alexi A. Wright, MD, MPH, of Harvard Medical School and Dana-Farber Cancer Institute in Boston, told Reuters. "The best way to do this is to encourage patients, physicians and family members to talk about their end-of-life wishes." **EBO**

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FDA Advocates More Diversity in Clinical Trials

SURABHI DANGI-GARIMELLA, PHD

Historically, the design of clinical trials to evaluate specific drugs has been in a controlled environment. The study population enrolled in a trial is very carefully chosen, with specific inclusion and exclusion criteria for trial subjects. However, in the real world, the drug will be prescribed to a diverse population of patients, each with a distinct genetic profile that can result in significant differences in drug exposure, absorption, metabolism, outcomes, and adverse effects.

Several studies have noted the lack of diversity in clinical trials. Physicians usually base their treatment decisions by extrapolating the results of trial data from a relatively homogenous population of white males. With a near-equal split in the percentage of males and females in the US, and with racial and ethnic minorities making up nearly 40% of the population, heterogeneity in clinical trials would be extremely valuable. Another population that is often underrepresented in clinical trials are the elderly. Medications developed for chronic conditions are typically used by the elderly, and the 65-plus is the fastest growing segment of the global population.

A study conducted by researchers at the University of California, Davis, found that while cancer clinical trial participation is low for all adult groups (3-5%), the percentage of minorities who participate in clinical trials is not representative of the US population affected by cancer. For example, blacks experience the highest incidence of cancer (593.7 cases per 100,000 people) but, along with Hispanics, have the lowest rates of cancer clinical trials participation at 1.3%.[1]

Responding to these concerns, the FDA, under direction by the Congress, has been paying greater attention to study subject diversity in clinical trials. The directive from the Congress was included in Section 907 of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, and in response, the FDA created the Drug Trial Snapshot,[2] which provides details on the demographic profiles of participants in clinical trials of approved drugs. The Snapshot would thereby be the go-to page for patients and providers alike to understand the responses of specific groups of patients to these drugs.

Including more women, minorities, and the older population in a trial can help drug developers as well as providers better understand clinical presentation and response to the drug being developed in a wider demographic.

This effort can have a tremendous impact on the quality of care as well as downstream costs of care for the health system as a whole. Inclusion of more women, minorities, and the older population in a trial can help drug developers as well as providers better understand clinical presentation and response to the drug being developed in a wider demographic. A skewed pool of participants could miss important drug-gene interactions. A clear understanding of a drug's effects across the population can potentially reduce experimentation by physicians once the drug is approved for use in the clinic.

To that end, the FDA is planning numerous efforts in 2016 to push for greater inclusion in trial populations:

- FDA's Office of Minority Health has developed tools to support clinical trial participation, including collaboration with the National Library of Medicine to raise consumer and patient awareness on clinical trials
- FDA's Office of Women's Health launched its Diverse Women in Clinical Trials initiative to raise awareness and share best practices about clinical research design, recruitment, and subpopulation analyses
- Ongoing efforts to engage patient advocacy groups in clinical trial design, feedback, and evaluation
- FDA staff will work with the research community to refine their approach to the conduct and analysis of trials to provide the best estimates of treatment effects for diverse populations.

What is needed is a concerted effort from various agencies and policy changes to push greater inclusion and avoid disparities in clinical trials. **EBO**

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Smoking Can Reduce Survival of Breast Cancer Patients

SURABHI DANGI-GARIMELLA, PHD

A study published in the *Journal of Clinical Oncology* has found that smoking before and after diagnosis of breast cancer is associated with increased mortality from breast cancer as well as other conditions, including respiratory and cardiovascular disease.[1]

For this Collaborative Breast Cancer and Women's Longevity Study, women were recruited from across the states of Wisconsin, New Hampshire, and Massachusetts for a prospective evaluation of the association between smoking status before and after breast cancer diagnosis and mortality. Nearly 20,700 women between the ages of 20 and 79 years, who were diagnosed with incident localized or regional invasive breast cancer between 1988 and 2008, participated in the study. Participants were asked to report on their smoking habits and the age when they started smoking. The women were followed for a median duration of 12 years following diagnosis.

During the 12-year follow-up period of the study, 6778 women died, including 2894 who died of breast cancer. The study found that women who smoked a year before their breast cancer diagnosis were more likely to die of breast cancer than women who never smoked (hazard ratio [HR], 1.25; 95% CI, 1.13-1.37). Other likely causes of death in this population were respiratory cancer (HR, 14.48; 95% CI, 9.89-21.21), other respiratory disease (HR, 6.02; 95% CI, 4.55-7.97), and cardiovascular disease (HR, 2.08; 95% CI, 1.80-2.41). Mortality due to breast cancer was highest among long-term smokers, heavy smokers, or former smokers who quit less than 5 years before being diagnosed, the authors report.

Further, the authors report that 1 in 10 study participants who did not quit following their diagnosis were more likely to die of breast cancer than those who never smoked (HR, 1.72; 95% CI, 1.13 to 2.60), or those who quit smoking following their cancer diagnosis. Women who quit had lower mortality from breast cancer (HR, 0.67; 95% CI, 0.38 to 1.19) and respiratory cancer (HR, 0.39; 95% CI, 0.16 to 0.95), the study found.

According to lead author Michael Passarelli, PhD, these results should motivate women who have been diagnosed with breast cancer to quit smoking if they still do. "Our study shows the consequences facing both active and former smokers with a history of breast cancer," he said in a related press release, adding, "Smoking cessation programs should be considered part of cancer therapy. Recent policy statements from leading research and clinical organizations are now urging oncologists to be as aggressive in getting their patients to stop smoking as they are in treating the cancer."

Physician organizations like the National Comprehensive Cancer Network (NCCN) have taken the lead in urging oncologists to speak to their patients about quitting. "Once patients have been diagnosed with cancer, they think quitting smoking is not worth it, but there are health benefits of smoking cessation that apply to patients in any stage of cancer," said Peter G. Shields, MD, deputy director of The Ohio State University Comprehensive Cancer Center, when introducing the Guidelines at the NCCN meeting last year. **EBO**

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Who Should Lead the Shared-Care Cancer Survivorship Model?

SURABHI DANGI-GARIMELLA, PHD

With a growing number of cancer survivors in the United States (about 12 million by current estimates), there is increasing pressure on primary care physicians (PCPs) to share responsibilities of follow-up care with the patient's oncologist. However, several studies, including one that was recently presented at the 2016 Cancer Survivorship Symposium hosted by the American Society of Clinical Oncology (ASCO), have found significant uncertainty on who is responsible for the care of cancer survivors, which can lead to care gaps that affect health outcomes.

Researchers at the University of Texas compared the attitudes and practices of PCPs and oncologists in an integrated healthcare system that shares a common electronic health record and clinical infrastructure. The hypothesis was that an integrated system might provide an adequate setup for clinicians to help coordinate survivor care responsibilities. The results, however, suggested otherwise.

Analyzing the results of their survey of 41 PCPs and 24 oncologists who were affiliated with the integrated system, the researchers found that 41% of PCPs preferred an oncologist-led care delivery model as compared with 21% of oncologists. Nearly 75% of PCPs believed in their ability to initiate cancer surveillance, while a majority (58%) of oncologists thought otherwise. Despite their belief in their own skills, PCPs preferred to take the back seat when it came to follow-up care of cancer survivors, with 56% advocating for the oncologist to lead the process, as opposed to 42% of oncologists wanting to do it.[1]

"What we found is that both agree that primary care physicians have the skills to care for these patients. There is agreement there, but it's still a new problem for the health system. But when you ask about the preferred model, the PCPs do not want a primary-care-led model," Bijal A. Balasubramanian, MBBS, PhD, lead author on the study, told Medscape Medical News. "We haven't yet figured out how to deliver this shared-care model, and clearly there are many problems associated with it."

The 2 clinician groups also held distinct opinions on cancer surveillance practices, with oncologists consistently reporting that PCPs ordered tests for cancer surveillance, evaluated patients for cancer recurrence and for adverse physical and psychological effects of cancer or its treatment, as well as managed pain and adverse outcomes of cancer treatment. PCPs, however, did not agree on equivalent ordering of these services.

According to Balasubramanian, there is need to develop improved communication methods between the oncologists and PCPs to avoid the potential gap in care of survivors.

It's important to note that the issues that the study has identified were observed within an integrated healthcare system. If one steps out into the community clinic arena, there is probably a bigger void between oncologists and PCPs that needs to be filled.

With this in mind, ASCO and the American Cancer Society recently released guidelines (for breast cancer) to help PCPs better manage potential long-term and late effects and to provide timely and appropriate screening and surveillance to improve the overall health and QoL of survivors.[2] Additionally, online training modules, such as the Cancer Survivorship Training (developed under guidance of the University of Kansas), are being offered to healthcare professionals to help transition survivors back to their PCPs. **EBO**

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