Bridging the gap between payer and provider perspectives

July 2015
Volume 21
Special Issue 10

THE AMERICAN JOURNAL OF MANAGED CARE®

20 YEARS OF RESEARCH · 20 YEARS OF LEADERSHIP
20TH ANNIVERSARY
1995-2015

Evidence-Based Oncology

ASCO Annual '15 Meeting

MAY 29-JUNE 2 • CHICAGO, IL | EXCLUSIVE CONFERENCE COVERAGE

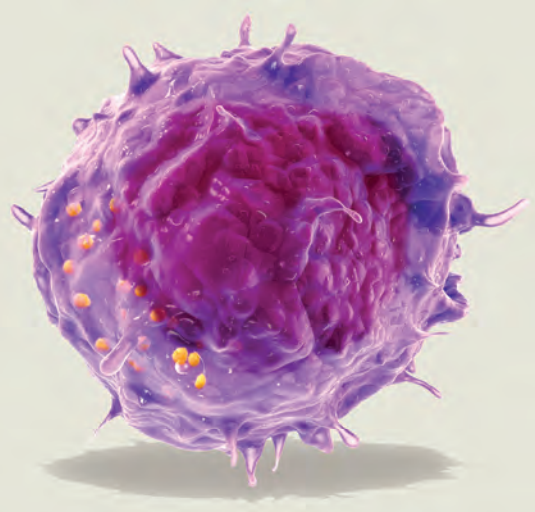
Highlights Include:

- Predictive biomarker results with immuno-oncology agents
- Novel treatment agents in melanoma and multiple myeloma
- Multiple stakeholders discuss their understanding of the value of cancer care
- Advanced clinical trial designs to optimize outcomes and improve access
- With increased emphasis on quality, physicians struggle with administrative burdens

THERE'S A NATURAL KILLER INSIDE EVERYONE

WITH THE POTENTIAL TO TAKE ON MULTIPLE MYELOMA

Natural Killer Cells play an important role in the immune response to multiple myeloma.[1] However, disease burden increases as myeloma cells evolve to evade and suppress the body's natural immune response.[1-9]



Immuno-oncology is a fundamentally different modality under investigation for multiple myeloma and Bristol-Myers Squibb is researching the potential of the **SLAMF7, KIR,** and **CD137** pathways to activate the body's own Natural Killer Cells to target myeloma cells.

Rethink Multiple Myeloma

Bristol-Myers Squibb is deeply committed to furthering the science behind immuno-oncology by rethinking research and emphasizing the importance of a comprehensive approach to endpoint evaluation in multiple myeloma.

www.RethinkMultipleMyeloma.com

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Bristol-Myers Squibb

Immuno-Oncology

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

06/15 PRC-01166

pharmacyclics®
An AbbVie Company

janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

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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and
Marketed by:
Janssen Biotech, Inc.
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Michael J. Hennessy Associates, Inc.

Office Center at Princeton Meadows, Bldg. 300
Plainsboro, NJ 08536 • (609) 716-7777

The American Journal of Managed Care ISSN 1088-0224 (print) & ISSN 1936-2692 (online) is published monthly by Managed Care & Healthcare Communications, LLC, 666 Plainsboro Rd, Bldg. 300, Plainsboro, NJ 08536.

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All Things Oncology, All in 1 Place


MIKE HENNESSY, SR

The annual meeting of the American Society of Clinical Oncology (ASCO) is becoming more and more of a melting pot for stakeholders from all realms of oncology: clinical researchers and physicians, basic research scientists, oncologists, pharmaceutical, biotechnology, and diagnostic industry representatives, patient advocates—the list seems endless.

Again this year, about 30,000 global participants convened in Chicago's McCormick Place to discuss all things oncology. While immuno-oncology was still at the top of the agenda, same as last year, this meeting buzzed with additional interest in CancerLinQ, the platform developed by ASCO that will connect providers all around the country and allow them to share real-time patient data, as well as identify trends and patterns and provide clinical decision support tools.

The wave of immuno-oncology data continues to impress, but the emphasis is now on correlating response to biomarker expression. As you'll read in this special issue, while expression of some biomarkers such as PD-1 and PD-L1 still shows variability with respect to clinical outcomes, expression of proteins in the mismatched repair-deficient tumors responded well to PD-1 inhibition, specifically in colorectal cancer. While this might seem a tremendous undertaking—improving the granularity of response to a single agent, in a specific tumor type, harboring a particular mutation—scientists are already working on this by modifying clinical trial designs. Three experts, representing the National Cancer Institute, the Mayo Clinic, and the Dana-Farber Cancer Institute, provided a detailed picture of new trial designs during an educational session in which they explained how the MATCH, I-SPY2, and Lung-MAP trials are paving the way for quicker patient access to newer treatments.

The meeting also served as a platform for oncologists to discuss the growing administrative burden brought on by the increasing emphasis on healthcare quality and outcomes-based reimbursement. A very popular session was a panel discussion, with diverse representation, on the "value" of cancer care. While opinions differed, the session highlighted the need for an integrated team to develop a healthcare framework for cancer patients.

We hope that this special issue provides a flavor of the annual meeting, and we thank you for your readership. Please stay updated on conferences and *AJMC* events by visiting www.ajmc.com/conferences.

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.

Predictive Biomarkers Present Promise in Immuno-Oncology

Surabhi Dangi-Garimella, PhD

A late-breaking abstract session early on the second day of the annual meeting of the American Society of Clinical Oncology was reserved for the latest data from clinical trials evaluating the new immuno-oncology agents of the PD-1 inhibitor class. Trial data were presented for nivolumab (Opdivo) in the treatment of hepatocellular carcinoma (HCC), non-squamous cell non-small cell lung cancer (NSCLC), and for tumors harboring mismatch repair deficiency.

Neil Segal, MD, PhD, of Memorial Sloan Kettering Cancer Center, moderated this standing room only session. He highlighted several milestones in the field, starting with the approval of ipilimumab in 2010 for advanced melanoma, nivolumab and pembrolizumab in 2014 for patients who have progressed on ipilimumab in melanoma, and finally the recent approval of nivolumab in 2015 for NSCLC patients who have progressed on chemotherapy.

Segal then introduced the first speaker, Dung T. Le, MD, assistant professor of oncology at The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. During her presentation, "PD-1 blockade in tumors with mismatch repair deficiency," Le introduced the much-discussed trial that could help predict response to PD-1 blockade in colorectal cancer (CRC) patients.

The hypothesis of the study, Le said, was that immune augmentation with PD-1 blockade may be highly effective in mismatch repair deficient tumors. Mismatch repair deficiency (MMRD) causes microsatellite instability, which, Le said, could stem from germline or somatic mutations, or epigenetic silencing. Importantly, MMRD is associated with multiple tumor types and, therefore, could be a good target.

She then went on to describe the phase 2 study conducted to evaluate the clinical activity of the anti–PD-1 monoclonal antibody, pembrolizumab, in 41 patients—with and without MMRD—who had previously treated progressive metastatic disease. The patients were divided into 3 cohorts: cohort A, CRC patients deficient in mismatch repair; cohort B, CRC patients proficient in mismatch repair; and cohort C, non-CRC patient deficient in mismatch repair. The primary end points, said Le, were immune-related objective response rate (irORR) and immune-related progression-free survival (irPFS) at 20 weeks. A majority of the patients enrolled had 2 or more prior therapies.

At 20 weeks, the irORR for cohort A was 62% and the disease control rate (DCR) was 92%; for cohort B, the irORR was 0% and DCR was 16%; for cohort C, the irORR was 60% and DCR was 70%.

Le showed that durable disease control was achieved in cohort A, with most responses lasting over a year. While progression-free survival (PFS) had not been reached in cohorts A and C, PFS was 2.3 months in cohort B. Adverse events observed were primarily of low grade.

In the MMRD CRC cohort, a high mutation burden was observed, which Le said was associated with PFS. This, she said, suggests that MMRD status predicts the clinical benefit of immune checkpoint blockade with pembrolizumab, and based on these results, Merck will be initiating the Keynote-164 trial. "Genomic data is more influential than histology for mismatch repair deficient tumors treated with an anti-PD-1 inhibitor," she concluded.

Dr Paz-Ares presents data from the CheckMate-057 trial.
Photo: ASCO.

The next presentation by Anthony B. El-Khoueiry, MD, assistant professor of clinical medicine and clinical instructor at the University of Southern California Norris Comprehensive Cancer Center, shared results of a phase 1/2 safety and antitumor study of nivolumab in patients with advanced HCC.

HCC is the second-most frequent cause of cancer-related death, he said, and sorafenib is the standard of care for advanced HCC. There is no second-line option available for patients whose disease progresses following sorafenib treatment. Median survival with supportive care in these patients is 6 to 10 months. El-Khoueiry showed that hepatitis B and C infection upregulates PD-1 expression levels, and increased PD-1 and PD-L1 expression in HCC is associated with poor prognosis. Since nivolumab blocks the interaction of PD-1 on T-cells with the PD-L1 ligand secreted by tumor cells, their group evaluated the inhibitor in HCC patients, he said.

The primary objective of this phase 1/2 study, said El-Khoueiry, was to evaluate the safety, tolerability, dose-limiting toxicity, and maximum tolerated dose of nivolumab in HCC. The secondary objective was to evaluate its antitumor activity.

Most patients in the trial had received prior therapy, radiotherapy, or local treatment for HCC; 68% of patients had prior treatment with sorafenib.

ORR was determined using RECIST-1 criteria in the 42 (of 47) evaluable patients, and was 19%, he showed; CR was 5% across all cohorts. Several patients also had a reduced tumor burden (40% of patients). Additionally, he showed that a durable response of 9 months or longer was observed in 7 patients. Overall survival (OS) at 9 months was 70%.

El-Khoueiry pointed out that clinical responses were observed across different dose levels in this study—even at very low doses—which is also observed with other PD-1 and PD-L1 agents.

The final presentation was the phase 3 results of CheckMate-057, which compared nivolumab with docetaxel in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC). Luis G. Paz-Ares, MD, PhD, an oncologist with Hospital Universitario Doce de Octubre, Spain, said that the options for advanced non-SQ NSCLC patients who have progressed after platinum-based doublet chemotherapy are limited, with minimal improvement in OS.

Therefore, to evaluate nivolumab as an option in these patients, they conducted a global phase 3 study of nivolumab against docetaxel in patients with advanced non-SQ NSCLC, said Paz-Ares.

The primary objective of the study was OS, and secondary objectives were investigator-assessed ORR, PFS, efficacy by PD-L1 expression, quality of life, and safety.

Paz-Ares showed data confirming that the trial met its end points. Median survival improved by 2.7 months with nivolumab, ORR with nivolumab was 19.2% versus 12.4% with docetaxel, and median PFS was 4.2 months versus 2.3 months with docetaxel.

Overall, the incidence and severity of adverse events were lower with nivolumab than docetaxel, said Paz-Ares. The trial showed that PD-L1 expression is predictive of benefit with nivolumab—median OS nearly doubled with nivolumab treatment compared with docetaxel across the PD-L1 expression continuum, he said. **EBO**

ABOUT THE PRESENTERS

DUNG T. LEE, MD

Dr Lee is assistant professor of oncology at the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins.

LUIS G. PAZ-ARES, MD, PHD

Dr Paz-Ares is an oncologist at Hospital Universitario Doce de Octubre, Spain.

NEIL SEGAL, MD, PHD

Dr Segal is a medical oncologist at Memorial Sloan Kettering Cancer Center.

Choosing the Ideal Lymphoma Regimen

Surabhi Dangi-Garimella, PhD

ABOUT THE PRESENTERS

GILLES A. SALLES, MD, PHD

Dr Salles is professor, Hospices Civils de Lyon, Université Claude Bernard.

STEPHEN M. ANSELL, MD, PHD

Dr Ansell is professor of medicine, Mayo Clinic.

While a number of active therapies are available to treat lymphoma, several new agents have been approved for this setting. There is a critical need to increase awareness of how these new agents fit into everyday practice and to discuss end points and goals of treatment. On the first day at the annual meeting of the American Society of Clinical Oncology in Chicago, physicians introduced some of the newer agents and described their personal experiences with using them during the session, "Incorporating Novel Agents Into Lymphoma Therapy: Value in Everyday Practice."

Gilles A. Salles, MD, PhD, from the Hospices Civils de Lyon, Université Claude Bernard, introduced the audience to the treatment regimens being developed for follicular lymphoma (FL). Following the success of rituximab, several failed attempts at developing anti-CD20 antibodies have been made. Salles said that a phase 2 study of ofatumumab in rituximab-refractory FL patients was conducted, but the overall response rate (ORR) was disappointing, with only 11% of patients responding. A head-to-head study of rituximab versus obinutuzumab (GA101) showed no difference, he explained. Antibodies against a few other target proteins—CD22, CD80, CD74, and CD37—are also being developed, he added.

A characteristic of FL, according to Salles, is a defective immune response in tumors; specifically, tumor-infiltrating lymphocytes from FL have an impaired synapse formation. Treatment with lenalidomide and IMiDs (analogues of thalidomide) can abolish this effect.

Using lenalidomide as a single agent in patients with relapsed refractory FL resulted in 27% ORR and 9% complete response (CR), said Salles; however, the treatment can cause neutropenia and may require a dose reduction of lenalidomide. Other commonly encountered side effects include rash, pain, and fatigue. A combination trial that evaluated lenalidomide and rituximab as frontline therapy in FL has yielded much better results: 98% ORR, with 85% patients reaching CR and 13% patients having a partial response.

Introducing the most sought after agents in oncology, Salles said that T-cell activity can be blocked by inhibiting the PD-1/PD-L1 interaction. When the anti-PD-1 monoclonal antibody pidilizumab was combined with rituximab in FL, more than 50% of patients achieved ORR, which he described as very encouraging.

Some other signaling pathways being targeted in FL, he showed, include PI3K and BTK, and inhibitors against these molecules are under clinical development. For example, Salles showed that idelalisib, which inhibits PI3K-d, demonstrated rapid, durable responses and acceptable safety in highly refractory, relapsed FL patients in a phase 2 study. ORR was 56%, CR was 6%, duration of response was 12.5 months, and the most common adverse events were diarrhea, cough, pyrexia, fatigue, and nausea.

In everyday practice, however, Salles recommended caution when using these agents as first-line therapy. There are several options that can present good quality-of-life for patients, he said, adding that radiation is still an option for localized disease. But toxicity and the cost of these agents should be considerations when patients have a low tumor burden. For patients with a high tumor burden, he said, R-CHOP with chemotherapy is used.

Among relapsed/refractory patients, autologous and allogenic transplant is an option for younger patients, while for others, chemotherapy-free regimens are a definite option.

To discuss Hodgkin lymphoma (HL) and agents developed to treat the condition was Stephen M. Ansell, MD, PhD, professor of medicine at the Mayo Clinic in Minnesota. He began his talk on a very encouraging note, saying, "These are exciting times for Hodgkin lymphoma."

HL, said Ansell, has a unique histology which provides multiple targeting options: signaling pathways, cell surface receptors, intra-tumoral immune cells, and intra-tumoral cytokines.

Some of the novel agents currently being evaluated in the clinic, he said, include the monoclonal antibody brentuximab vedotin. One study found that brentuximab vedotin treatment resulted in 75% ORR and 34% CR, and the treatment was reasonably well tolerated. When brentuximab vedotin was incorporated into the A(B)VD (Adriamycin, bleomycin, vinblastine, dacarbazine) regimen—a first-line chemotherapy regimen used in HL—a durable response rate was observed, and progression free survival was about 80%, which is quite promising.

> *"Using lenalidomide as a single agent in patients with relapsed refractory follicular lymphoma resulted in 27% ORR and 9% CR. However, the treatment can cause neturopenia and may require a dose reduction of lenalidomide. Other commonly encountered side effects include rash, pain, and fatigue."*
>
> —GILLES A. SALLES, MD, PHD

Use of PD-1 agents is a promising treatment approach in HL. PD-1 is expressed on activated T-cells in the tumor as well as intra-tumoral macrophages and monocytes, said Ansell. Using nivolumab in HL patients resulted in a 70% PR and 17% CR. Overall, said Ansell, nivolumab was well tolerated, and a durable response was observed.

When the other approved PD-1 inhibitor antibody, pembrolizumab, was evaluated in a small study with 29 patients, he said, the majority of patients had a good and durable response to treatment.

Ansell then talked about a few other promising agents being evaluated in the clinic, such as the HDAC (histone deacetylase) inhibitor panobinostat (LBH589), which yielded an ORR of 27%.

Lenalidomide, used to treat FL, is promising in HL as well. It targets the malignant cells, T cells, and other immune components, in addition to stromal effects.

"Multiple new approaches have promising activity in HL patients," Ansell said. "The future, though, is in the use of combination treatment with standard chemotherapy." **EBO**

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

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OPDIVO™ (nivolumab)

Expect More. Do More.

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

INDICATION

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

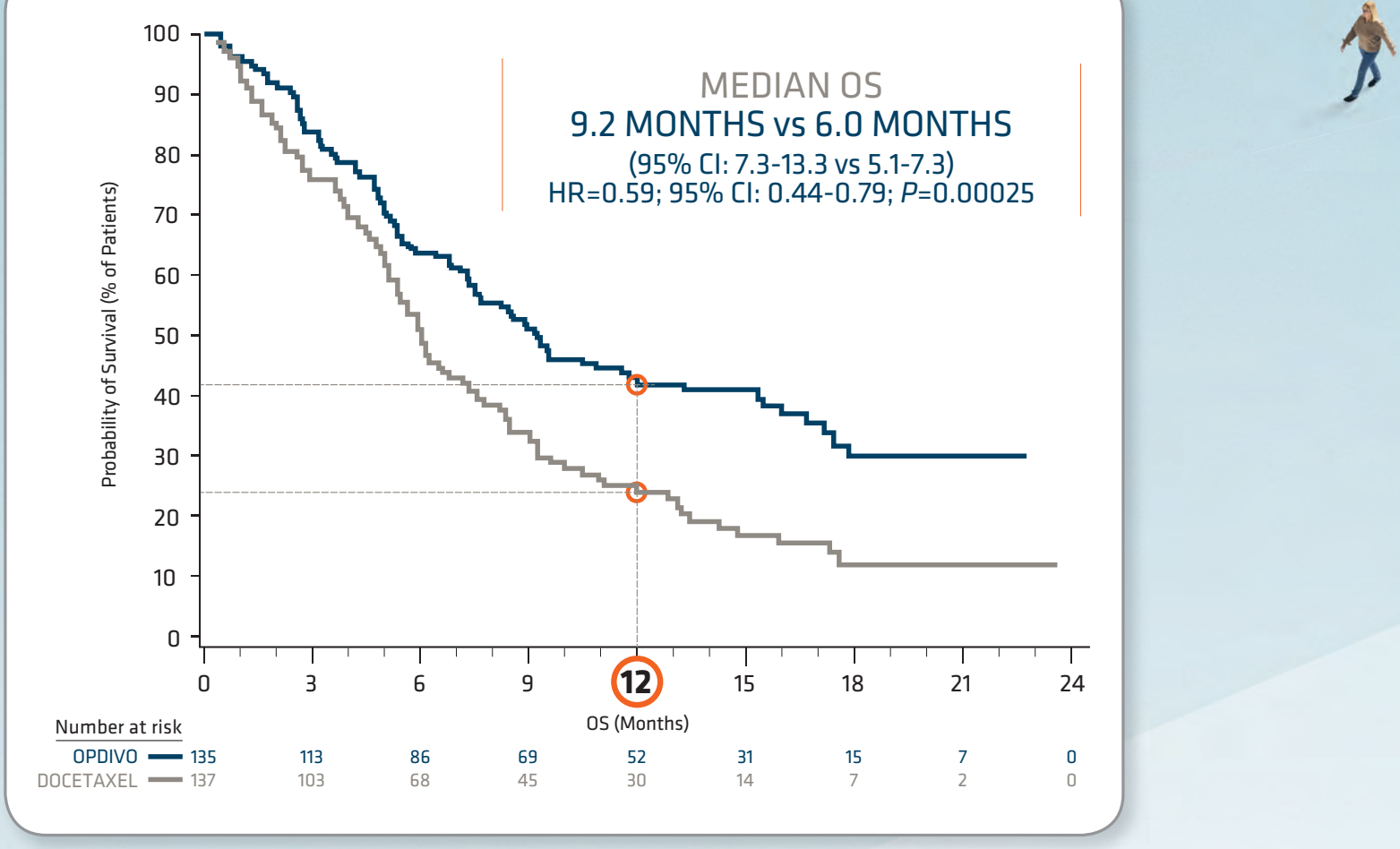
SELECT IMPORTANT SAFETY INFORMATION

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

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

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

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



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

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

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

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

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

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

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

Serious Adverse Reactions

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

Common Adverse Reactions

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

Please see additional Important Safety Information on the following page.

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FOR LIVE SUPPORT AND ASSISTANCE
8:00 AM to 8:00 PM ET, Monday-Friday

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IMPORTANT SAFETY INFORMATION

Immune-Mediated Pneumonitis

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

Immune-Mediated Colitis

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

Immune-Mediated Hepatitis

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

Immune-Mediated Nephritis and Renal Dysfunction

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

Immune-Mediated Hypothyroidism and Hyperthyroidism

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

Other Immune-Mediated Adverse Reactions

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

Embryofetal Toxicity

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

Lactation

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

Serious Adverse Reactions

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

Common Adverse Reactions

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

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

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

OPDIVO™
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Bristol-Myers Squibb

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

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Immune-Mediated Pneumonitis

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

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

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

Immune-Mediated Colitis

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

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

Immune-Mediated Hepatitis

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

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

Immune-Mediated Nephritis and Renal Dysfunction

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

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

Immune-Mediated Hypothyroidism and Hyperthyroidism

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

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

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

Other Immune-Mediated Adverse Reactions

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

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

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

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

Embryofetal Toxicity

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

ADVERSE REACTIONS

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

- Immune-Mediated Pneumonitis *[see Warnings and Precautions]*
- Immune-Mediated Colitis *[see Warnings and Precautions]*
- Immune-Mediated Hepatitis *[see Warnings and Precautions]*
- Immune-Mediated Nephritis and Renal Dysfunction *[see Warnings and Precautions]*
- Immune-Mediated Hypothyroidism and Hyperthyroidism *[see Warnings and Precautions]*
- Other Immune-Mediated Adverse Reactions *[see Warnings and Precautions]*

Clinical Trials Experience

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

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

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

Metastatic Squamous Non-Small Cell Lung Cancer

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

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

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

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

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

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

(Continued)

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

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

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

General Disorders and Administration Site Conditions: stomatitis

Nervous System Disorders: peripheral neuropathy

Infections and Infestations: bronchitis, upper respiratory tract infection

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

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

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

Immunogenicity

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

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

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Contraception

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

Pediatric Use

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

Geriatric Use

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

Renal Impairment

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

Hepatic Impairment

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

OVERDOSAGE

There is no information on overdosage with OPDIVO.

PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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1321663A1 Revised: March 2015

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Targeted Therapies IN ONCOLOGY

Information on some early-phase studies with alternate agents in multiple myeloma can be obtained at **http://bit.ly/1LG199j**.

Elotuzumab Combo Delays Myeloma Progression in Phase 3 Trial

Jason M. Broderick

ABOUT THE LEAD AUTHOR

SAGAR LONIAL, MD

Dr Lonial is chief medical officer, Winship Cancer Institute, Emory University.

Adding elotuzumab to lenalidomide (Revlimid) and dexamethasone reduced the risk of disease progression by 30% in patients with relapsed-refractory multiple myeloma (RRMM), according to interim results from the phase 3 ELOQUENT-2 trial. The data, which were presented during a presscast held in advance of the 2015 annual meeting of the American Society of Clinical Oncology (ASCO), showed that combining the monoclonal antibody with standard care prolonged remission by 4.5 months.

"Based on this randomized phase 3 trial, we hope that we will soon have a new treatment option for patients with relapsed or refractory myeloma where an immune therapy–based approach can be added with lenalidomide and dexamethasone for the management of these patients," said lead author Sagar Lonial, MD, chief medical officer of the Winship Cancer Institute of Emory University and professor and executive vice chair of the department of hematology and medical oncology of Emory University School of Medicine.

Elotuzumab, which is being developed by Bristol-Myers Squibb and AbbVie, binds to the SLAMF7 protein found on the surface of both myeloma cells and natural killer lymphocytes in the immune system. "One of the unique attributes of elotuzumab is that it appears to have a dual mechanism through which it both targets the myeloma cell and appears to enhance the activation of natural killer cells," said Lonial.

The open-label phase 3 ELOQUENT-2 trial randomized 646 patients with RRMM to lenalidomide and dexamethasone alone (n = 325) or in combination with elotuzumab (n = 321). Elotuzumab was administered at 10 mg/kg intravenously, weekly for the first 2 cycles and then biweekly thereafter, and lenalidomide was dosed at 25 mg orally on days 1 to 21 of each cycle. Across the study, patients received 40 mg of oral dexamethasone in weeks without elotuzumab. During the weeks when elotuzumab was administered in the experimental arm, dexamethasone was dosed at 28 mg orally plus 8 mg intravenously. The cycle length for all 3 drug regimens was 28 days, and treatment was administered until disease progression or unacceptable toxicity.[1]

The median patient age in the trial was 66 years, and patients had received a median of 2 prior therapies (range, 1-3) including bortezomib (70%), thalidomide (48%), and lenalidomide (6%). Thirty-five percent of patients were refractory to their most recent therapy; however, no patients were lenalidomide-refractory. High-risk patient subgroups were identified, with 32% and 9% of patients having a 17p deletion (del[17p]) or t(4;14) translocation, respectively.[1]

> *"Based on this randomized phase 3 trial, we hope that we will soon have a new treatment option for patients with relapsed or refactory myeloma where an immunotherapy–based approach can be added with lenalidomide and dexamethasone for the management of these patients."*
>
> —SAGAR LONIAL, MD

The primary outcome measures for the study were progression-free survival (PFS) and overall response rate (ORR). Overall survival (OS) was a secondary end point. Tumor response was assessed every 4 weeks and survival was assessed every 12 weeks following disease progression.[1]

At a median follow-up of 2 years, PFS with the elotuzumab regimen was 19.4 months (95% CI, 16.6-22.2) vs 14.9 months (95% CI, 12.1-17.2) with lenalidomide and dexamethasone alone (hazard ratio [HR], 0.70; 95% CI, 0.57-0.85; *P* = .0004). The 1-year PFS for the elotuzumab and control arms was 68% and 57%, respectively, with the 2-year PFS rates increasing to 41% and 27%, respectively.[1]

"What I think is quite striking about this progression-free survival curve compared with many others that you may have seen or will see at the meeting, is that the 2 curves do not appear to come back together with longer follow-up," said Lonial. "This idea of the maintenance of benefit over time really speaks to the power of an immune-mediated based approach when we treat cancer. We've seen this, for instance, with PD-1 and other immune-based approaches."

The PFS benefit with elotuzumab in the overall study was observed across the high-risk del(17p) and t(4;14) subgroups. ORR was 79% with elotuzumab and 66% for the control group (*P* = .0002). The OS data for the trial are not yet mature.[1]

Elotuzumab was well tolerated overall, according to Lonial. "The improvement in clinical parameters occurred without a significant increase in adverse events or toxicities. In fact, there was no reduction in quality of life for the group receiving the 3 drugs."

At the time of the interim analysis, 35% of patients receiving the elotuzumab regimen and 21% of patients receiving lenalidomide and dexamethasone alone remained on therapy. Disease progression was the primary cause of discontinuation, accounting for 42% and 47% of patients stopping treatment in the experimental and control arms, respectively. Grade 3 and 4 adverse events occurring in ≥15% of patients in the elotuzumab arm were neutropenia (25%, vs 33% in the control arm) and anemia (15%, vs 16% in the control arm).

Ten percent of patients receiving elotuzumab had infusion reactions, the majority of which were grade 1 or 2 and manageable.

Elotuzumab received a breakthrough therapy designation from the FDA in May 2014 for use in combination with lenalidomide and dexamethasone for patients with multiple myeloma following 1 or more prior therapies.[2] There are currently no FDA-approved monoclonal antibodies for the treatment of multiple myeloma, and the ELOQUENT-2 results are the first to demonstrate a PFS benefit in this disease in a phase 3 study.

The ongoing phase 3 ELOQUENT-1 trial is examining the elotuzumab plus lenalidomide and dexamethasone regimen in the frontline setting for relapsed-refractory multiple myeloma.[3] Other ongoing trials are examining elotuzumab in various other combinations with existing therapies.

In a question-and-answer session following the ASCO presscast, Lonial was asked about the cost of a 3-drug regimen if the FDA eventually approves elotuzumab. Lonial responded that the OS data for the trial require another 6 months of maturity, but there are "encouraging" signals of an OS benefit, which would be critical to any assessment of economic value.

"To me it's really about where is the plateau on that curve. If we are increasing [survival] or potentially even curing a subset of patients through the addition of an immune-based approach in combination with lenalidomide [and dexamethasone], in many ways that changes the game. Obviously cost is one of the factors, but what's the benefit that you get at that price? That is where I think we need a little bit more follow-up." **EBO**

References

1. Lonial S, Dimopoulos MA, Palumbo A, et al. ELOQUENT-2: a phase III, randomized, open-label study of lenalidomide (Len)/dexamethasone (dex) with/without elotuzumab (Elo) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol*. 2015;(suppl): abstract 8508.

2. Bristol-Myers Squibb and AbbVie receive U.S. FDA breakthrough therapy designation for elotuzumab, an investigational humanized monoclonal antibody for multiple myeloma [press release]. http://news.bms.com/press-release/rd-news/bristol-myers-squibb-and-abbvie-receive-us-fda-breakthrough-therapy-designatio. Princeton, NJ, and North Chicago, IL: Bristol-Myers Squibb Company and Abbvie; May 19, 2014.

3. Phase III study of lenalidomide and dexamethasone with or without elotuzumab to treat newly diagnosed, previously untreated multiple myeloma (ELOQUENT - 1). ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT01335399. Accessed June 9, 2015.

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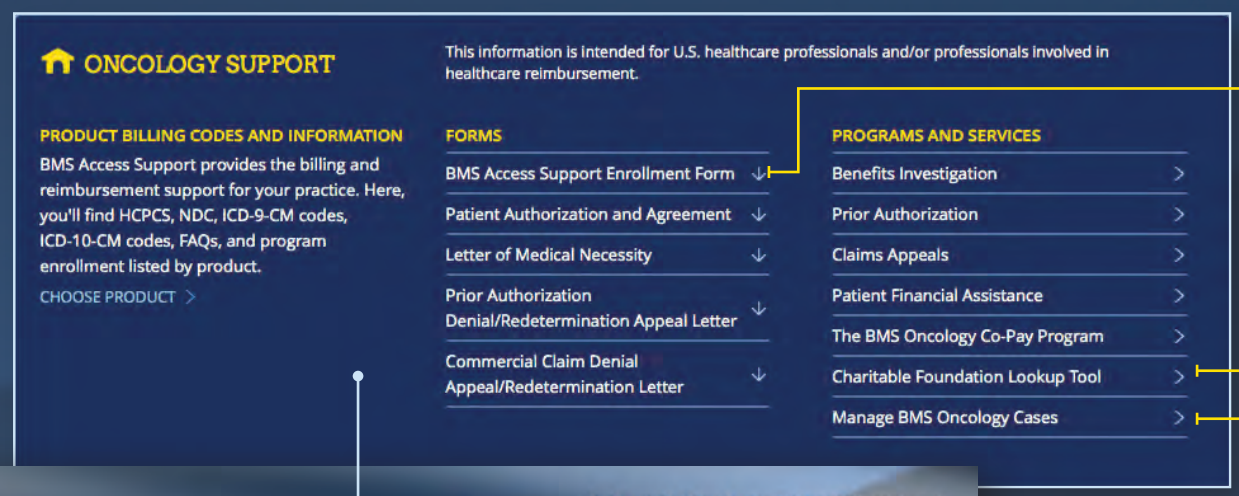

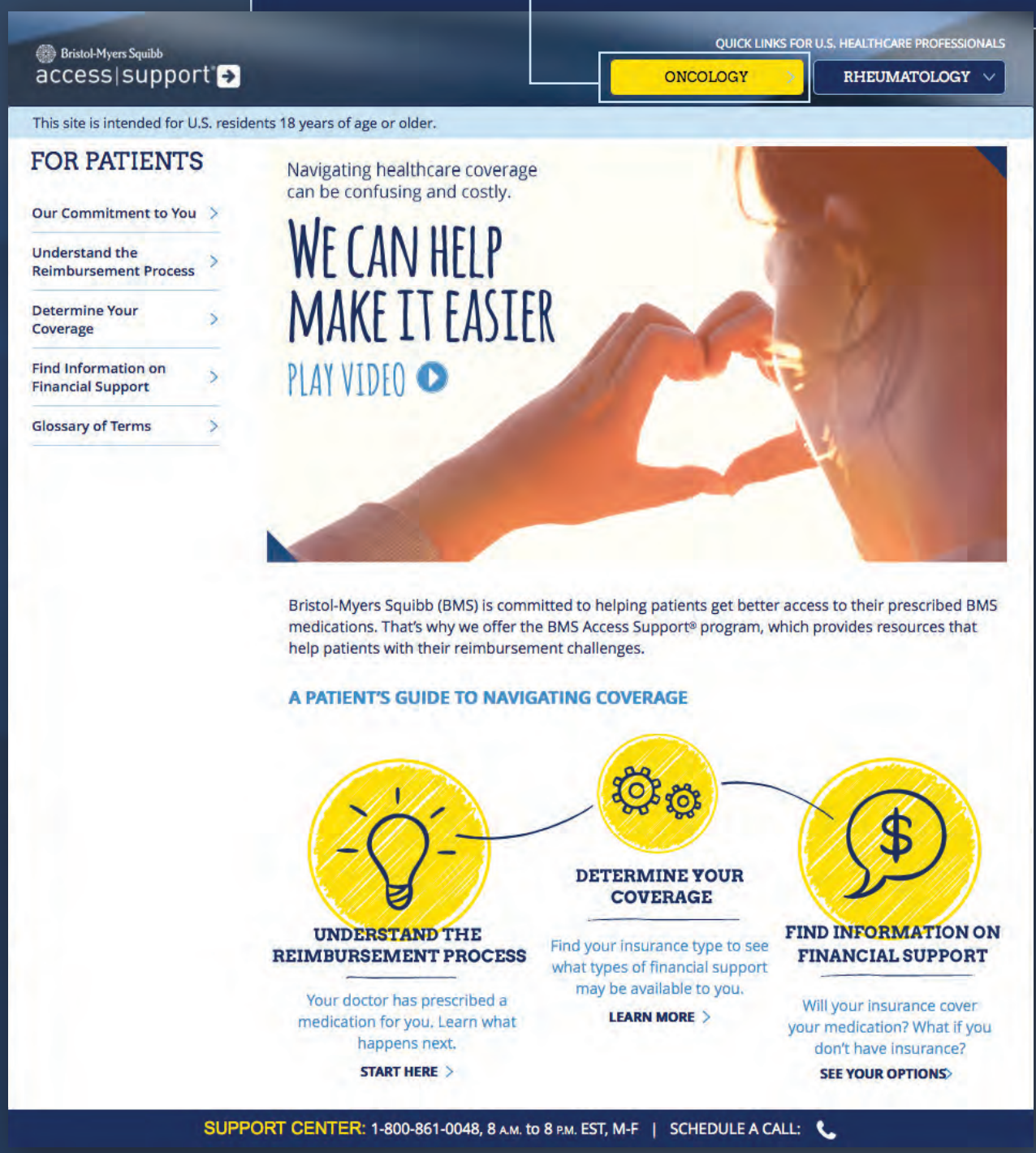

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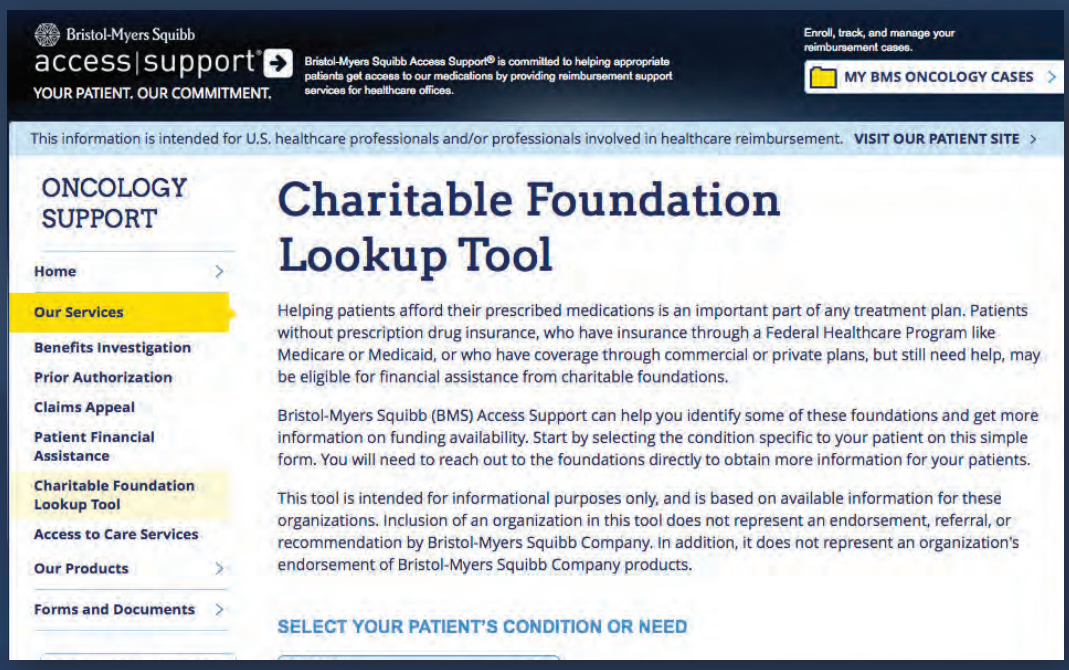

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ABOUT THE PRESENTER

JEDD D. WOLCHOK, MD, PHD

Dr Wolchok is chief, melanoma and immunotherapeutics service, Memorial Sloan Kettering Cancer Center.

TABLE. Primary and Secondary End Points in CheckMate 067 Trial

	NIVOLUMAB + IPILIMUMAB	NIVOLUMAB	IPILIMUMAB
PFS (months)*	11.5 (8.9-16.7)	6.9 (4.3-9.5)	2.9 (2.8-3.4)
ORR (%)*	57.6 (52.0-63.2)	43.7 (38.1-49.3)	19.0 (14.9-23.8)
CR rate (%)	11.5	8.9	2.2

CR indicates complete response; ORR, objective response rate; PFS, progression-free survival.
*PFS and ORR presented as median (95% CI).

CHECKMATE 67 RESULTS PUSH NIVOLUMAB CLOSER TO FIRST LINE IN MELANOMA

The much-anticipated phase 3 results from the CheckMate 067 trial were presented during the Plenary Session on the third day of the annual meeting of the American Society of Clinical Oncology, held at the McCormick Convention Center, Chicago, May 29-June 2, 2015. A late-breaking abstract, "Efficacy and Safety Results From a Phase III Trial of Nivolumab Alone or Combined With Ipilimumab Versus Ipilimumab Alone in Treatment-Naïve Patients With Advanced Melanoma," was presented by Jedd D. Wolchok, MD, PhD, chief, melanoma and immunotherapeutics service at Memorial Sloan Kettering Cancer Center.

CheckMate 67 is an ongoing randomized double-blind study designed to evaluate the efficacy of nivolumab as first-line therapy in advanced melanoma, alone or in combination with ipilimumab.

The trial methods were as follows: 945 treatment-naïve patients, a majority of whom were male, were randomized to receive either nivolumab alone, ipilimumab alone, or nivolumab and ipilimumab, until progression or unacceptable toxicity. Patients were stratified by PD-L1 status, BRAF mutation status, and disease stage. Primary end points were progression-free survival (PFS) and overall survival (OS). Secondary end points were objective response rate (ORR) and safety. During the Plenary Session, Wolchok reported PFS and ORR data (**TABLE**); the trial is ongoing to estimate OS.

At a minimum follow-up of 9 months, patients treated with the combination of nivolumab and ipilimumab, as well as those treated with nivolumab alone, had significantly improved PFS and ORR compared with patients treated with ipilimumab alone, said Wolchok.

Furthermore, a higher number of patients treated with the combination had a partial response compared with nivolumab or ipilimumab alone. While progressive disease was highest with ipilimumab and lowest with the combination, duration of response had not been reached because the follow-up period was not long enough.

When the response rate was analyzed in relation to high PD-L1 expression, Wolchok said that the combination treatment resulted in a higher response rate (72.1%) compared with nivolumab alone (57.5%). Similar trends were observed with low PD-L1-expressing tumors.

The safety profile of the combination, he said, was consistent with earlier results, and the combination did show a higher incidence of adverse events. There were no new safety signals or drug-related deaths observed with the combination, while the monotherapies had 1 death each. "The current evidence suggests that the combination presents a means to improve outcomes versus using nivolumab alone, especially in patients with low (<5%) PD-L1 expression," Wolchok concluded.

ELOTOZUMAB OFFERS PROMISE IN MULTIPLE MYELOMA

A poster presented on the second day of the annual meeting of the American Society of Clinical Oncology, held from May 29 to June 2, 2015, in Chicago, evaluated the advantage of incorporating the monoclonal antibody elotuzumab into a treatment regimen of bortezomib/dexamethasone in relapsed-refractory multiple myeloma (RRMM) patients. These results were from a phase 2 open-label study from 83 centers across the United States and Europe, and included 152 patients.[1]

Interaction of elotuzumab with the signaling lymphocytic activation molecule F7 results in myeloma cell death, with minimal effects on normal tissue. Previous studies from a preclinical myeloma model found enhanced activity of elotuzumab combined with bortezomib, as well as good phase 1 results. The current study investigated the efficacy and safety of elotuzumab ± bortezomib/dexamethasone in RRMM patients.

> *"At a minimum follow-up of 9 months, patients treated with the combination of nivolumab and ipilimumab, as well as those treated with nivolumab alone, had significantly improved PFS or ORR compared with patients treated with ipilimumab alone."*
>
> —JEDD D. WOLCHOK, MD, PHD

The primary objective of the study was to compare PFS between the treatment arms in the intent-to-treat population, and the secondary objective to estimate differences in response rates between the arms. Additionally, the researchers explored safety, time to response, duration of response, and OS.

Patients with RRMM who had progressed on 1, 2, or 3 prior therapies, and who met Eastern Cooperative Oncology Group status ≤ 2, were eligible for participation.[1]

The authors showed that the study met its primary end point of PFS: median PFS was 9.7 months in the elotozumab/bortezomib/dexamethasone–treated group versus 6.9 months when elotuzumab was left out. ORR was 65% when elotuzumab was included in the treatment versus 63% when it was not. The 1-year OS rate was 85% versus 74% with and without elotuzumab, respectively.[1]

At the time of analysis, 40 patients had died following disease progression, of which 17 were on the elotuzumab/bortezomib/dexamethasone arm. The authors did not see any differences in adverse events between the 2 trial arms.[1]

Based on this analysis, the authors concluded that the study met its primary end point. Elotuzumab significantly improved PFS when combined with bortezomib/dexamethasone, and elotuzumab-treated patients had a 28% reduction in their risk of disease progression. Additionally, the authors consider the available OS data encouraging as well. Long-term outcomes studies are ongoing.[1] **EBO**

Reference

1. Jakubowiak AJ, Offidani M, Pegourie B, et al. A randomized phase II study of bortezomib (Btz)/dexamethasone (dex) with or without elotuzumab (Elo) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol*. 2015;33(suppl): abstract 8573.

Stakeholder Definition of Value in Cancer: Where Are We 1 Year Later?

Surabhi Dangi-Garimella, PhD

Most alternate payment models being proposed today—whether generated by professional organizations like the American Society of Clinical Oncology (ASCO), by CMS, or by private payers—have an associated "value" attribute. While clinical data presented at the annual meeting of ASCO created waves, a session on value had an equally significant impact as throngs of oncologists came to hear stakeholder voices define this as yet abstract concept of "value" in cancer care. The session brought together a patient representative, an oncologist, an ASCO representative, and a payer.

ASCO'S VALUE INITIATIVE

Lowell E. Schnipper, MD, chief of hematology/oncology at the Beth Israel Deaconess Medical Center, provided his insight into ASCO's Value Initiative.

Defining clinically meaningful outcomes is the foundation of the Value Initiative, said Schnipper. He informed the audience that ASCO has invited multiple stakeholders to submit their comments on the initiative, with the objective of finding a meaningful balance among clinical benefit, side effects, and financial toxicity. He acknowledged that this is "a fairly difficult act." While metrics are essential to support these outcomes, said Schnipper, "The question is, 'What are the clinically meaningful outcomes and who defines them?'"

Schnipper went on to define some of the clinical trial end points most commonly used to ascertain clinical benefit: overall survival (OS), progression-free survival, palliation, and toxicity. Surrogates such as complete response and partial response, he said, are primarily used for breakthrough therapy designation by the FDA. While palliation is important in the advanced disease setting, he added, OS and disease free survival are important in the adjuvant setting, and toxicity is also a clinically important variable in advanced disease and in the adjuvant setting.

Of course, another important factor is cost. Schnipper said healthcare policy decisions can be made based on quality-adjusted life-years, which includes both the quality and the quantity of life post intervention in the value discussion.

ASCO, Schnipper said, is developing a value framework that can be implemented at the doctor-patient interface. ASCO plans to open up the framework for public feedback, with the objective of improving the tool.

ONCOLOGIST DEFINES VALUE OF CARE

Presenting the clinician's definition of value in cancer care was Neal J. Meropol, MD, professor and chief of the division of hematology/oncology at Case Western Reserve University School of Medicine. "I'll provide more of a physician perspective," he said, "based on what I hear from my patients about the cost or value of their treatment."

Among the commonly expressed concerns he listed were:

- The cost of traveling to the site of treatment
- Insurance coverage and co-payments
- Need for a specialty agent
- Denial of payment for recommended care.

> *"Our discussions today should not look at the influence on immediate [health] concerns; rather, they should help patients make informed decisions about their future—about their insurance coverage and deductibles and co-pays—which would impact healthcare overall."*
>
> —JENNIFER MALIN, MD

"Oncologists cannot be the gatekeepers based on cost; rather, we have the opportunity to be gatekeepers based on value," said Meropol.

He showed data from studies documenting that the out-of-pocket (OOP) costs in cancer care are greater than with other chronic diseases. Also, the rate of bankruptcies has been documented as being significantly higher among cancer patients than in individuals without a cancer diagnosis. OOP expenses, he said, have been associated with disparities in care. He cited as an example the fact that Medicare patients with private supplemental insurance have been shown to receive their required chemotherapy, while those without the private supplemental insurance have a lower probability of receiving it.

"Patients are open to communicating with their doctors about their cost burdens," said Meropol, and cost concerns may result in patients borrowing money from family or friends, draining their own retirement accounts, or making sacrifices to ensure continuity of treatment. There's racial disparity as well, he pointed out, and "economic hardship" was reported to be higher in minority populations in the first year of their cancer treatment.

However, Meropol noted, "A majority of patients, we need to keep in mind, have been shown to equate quality of life with length of life." They are also ready to pay for higher-value care if they are assured of better outcomes.

But what do oncologists think?

Meropol cited results of a study published in the *Journal of Clinical Oncology* nearly a decade ago, which suggested that 13% of surveyed oncologists did not have a good sense of their patient's monetary concerns as they underwent treatment. While 33% of the medical oncologists said they were not comfortable discussing cost, 25% did not discuss the financial aspects at all.[1] Economists hypothesize that physicians are incentivized by financial reimbursements, said Meropol. "To avoid these perverse incentives, we do need alternate payment models such as bundled payments, value-based insurance, and pay-for-performance."

Finally, Meropol highlighted some of the tools needed at the point of care to help providers make informed decisions when choosing "valuable" treatments:

1. What's the relative value of different treatment options?
2. What are the anticipated OOP costs for my patients?
3. What are my patient's goals and preferences?
4. What is the best way to communicate these issues to my patients?

THE PAYER'S VIEWPOINT

A third presenter at the session was Jennifer Malin, MD, staff vice president of clinical strategy at Anthem Inc, who discussed "Value From the Payer Perspective." According to Malin, the ultimate payer is the employer and/or the patient. "Our discussions today should not look at the influence on immediate [health] concerns; rather, they should help patients make informed decisions about their future—about their insurance coverage and deductibles and co-pays—which would impact healthcare overall," she said.

Malin introduced Anthem's clinical pathways program, which identifies high-value regimens to help curb treatment costs. Her organization, she said, views evidence from trials and publications; the information is then extracted, reviewed, and analyzed. Malin explained that external experts from various cancer centers and community

(continued on SP347)

ABOUT THE PRESENTERS

BEVERLY E. CANIN

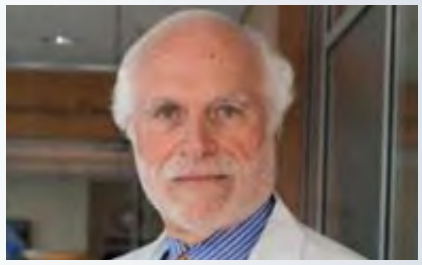
Ms Canin is president, Breast Cancer Options, Inc.

JENNIFER MALIN, MD

Dr Malin is staff vice president of clinical strategy, Anthem Inc.

NEAL J. MEROPOL, MD

Dr Meropol is professor and chief of the division of hematology/oncology, Case Western Reserve University School of Medicine.



LOWELL E. SCHNIPPER, MD

Dr Schnipper is chief of hematology/oncology, Beth Israel Deaconess Medical Center.

In mHRPC after docetaxel...

Don't Let the Window of Opportunity Close

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

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

Important Safety Information for JEVTANA®

WARNING: NEUTROPENIA AND HYPERSENSITIVITY

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

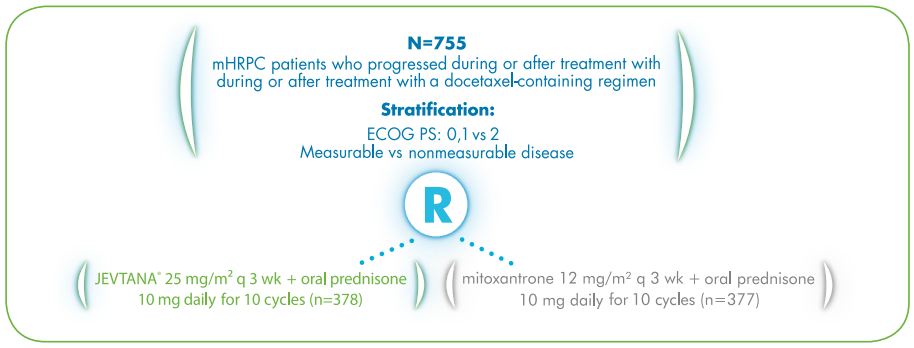
Please see additional Important Safety Information and Brief Summary of Full Prescribing Information, including boxed WARNINGS, on adjacent pages.

JEVTANA®
(cabazitaxel)
Injection

In mHRPC after docetaxel…

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

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



Endpoints[3]

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

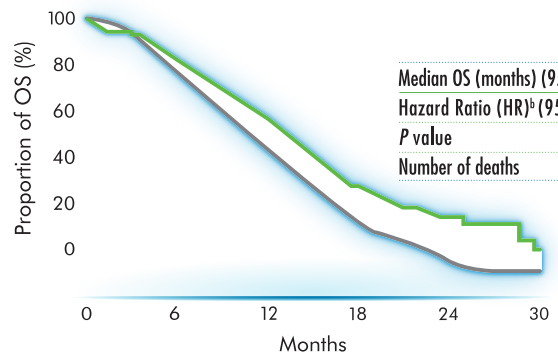
*For measurable disease according to RECIST criteria.
RECIST=Response Evaluation Criteria In Solid Tumors.

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

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

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

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



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

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

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

Important Safety Information for JEVTANA®

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

JEVTANA® (cabazitaxel) Injection Select Safety Information

Summary of hematologic AEs[1]

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

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

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

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

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

*Within 30 days of last study drug dose.

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

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

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

JEVTANA® (cabazitaxel) Injection

Important Safety Information for JEVTANA® (cabazitaxel) Injection

WARNING: NEUTROPENIA AND HYPERSENSITIVITY

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

US.CAB.15.01.001 1/15 Printed in U.S.A.

SANOFI ONCOLOGY

JEVTANA® (cabazitaxel) Injection

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

Brief Summary of Prescribing Information

WARNING : NEUTROPENIA AND HYPERSENSITIVITY

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

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

1. INDICATIONS AND USAGE

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

2. DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

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

2.2 Dose Modifications for Adverse Reactions

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

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

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

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

2.3 Dose Modifications for Drug Interactions

Strong CYP3A inhibitors

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

2.4 Premedication

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

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

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

2.5 Administration Precautions

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

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

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

2.6 Instructions for Preparation

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

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

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

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

Step 1 – First Dilution

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

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

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

Step 2 – Second (Final) Dilution

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

JEVTANA should not be mixed with any other drugs.

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

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

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

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

Discard any unused portion.

2.7 Administration

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

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

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

4. CONTRAINDICATIONS

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

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

5. WARNINGS AND PRECAUTIONS

5.1 Neutropenia

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

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

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

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

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

5.2 Hypersensitivity Reactions

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

5.3 Gastrointestinal Disorders

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

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

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

5.4 Renal Failure

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

5.5 Elderly Patients

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

5.6 Hepatic Impairment

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

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

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

5.7 Pregnancy

Pregnancy category D.

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

There are no adequate and well-controlled studies in pregnant women using JEVTANA. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during treatment with JEVTANA *[see Use in Specific Populations (8.1)]*.

6. ADVERSE REACTIONS

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

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

6.1 Clinical Trial Experience

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

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

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

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

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

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

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

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

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

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

*Graded using NCI CTCAE version 3
†Based on laboratory values, cabazitaxel: n =369, mitoxantrone: n = 370.
‡Includes atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block complete, bradycardia, palpitations, supraventricular tachycardia, tachyarrhythmia, and tachycardia.
§Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.
¶Includes gastroesophageal reflux disease and reflux gastritis.
#Includes urinary tract infection enterococcal and urinary tract infection fungal.
ÞIncludes peripheral motor neuropathy and peripheral sensory neuropathy.

Neutropenia and Associated Clinical Events:
Five patients experienced fatal infectious adverse events (sepsis or septic shock). All had grade 4 neutropenia and one had febrile neutropenia. One additional patient's death was attributed to neutropenia without a documented infection. Twenty-two (6%) patients discontinued JEVTANA treatment due to neutropenia, febrile neutropenia, infection, or sepsis. The most common adverse reaction leading to treatment discontinuation in the JEVTANA group was neutropenia (2%).
Hematuria:
Adverse events of hematuria, including those requiring medical intervention, were more common in JEVTANA-treated patients. The incidence of grade ≥ 2 hematuria was 6% in JEVTANA-treated patients and 2% in mitoxantrone-treated patients. Other factors associated with hematuria were well-balanced between arms and do not account for the increased rate of hematuria on the JEVTANA arm.
Hepatic Laboratory Abnormalities:
The incidences of grade 3–4 increased AST, increased ALT, and increased bilirubin were each ≤ 1%.
Elderly Population:
The following grade 1–4 adverse reactions were reported at rates ≥ 5% higher in patients 65 years of age or greater compared to younger patients: fatigue (40% vs. 30%), neutropenia (97% vs. 89%), asthenia (24% vs. 15%), pyrexia (15% vs. 8%), dizziness (10% vs. 5%), urinary tract infection (10% vs. 3%) and dehydration (7% vs. 2%), respectively.
The incidence of the following grade 3–4 adverse reactions were higher in patients ≥ 65 years of age compared to younger patients; neutropenia (87% vs. 74%), and febrile neutropenia (8% vs. 6%) *[see Use in Specific Populations (8.5)]*.

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

7. DRUG INTERACTIONS

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

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy category D. See 'Warnings and Precautions' section.
JEVTANA can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of JEVTANA in pregnant women.
Non-clinical studies in rats and rabbits have shown that cabazitaxel is embryotoxic, fetotoxic, and abortifacient. Cabazitaxel was shown to cross the placenta barrier within 24 hours of a single intravenous administration of a 0.08 mg/kg dose (approximately 0.02 times the maximum recommended human dose-MRHD) to pregnant rats at gestational day 17.
Cabazitaxel administered once daily to female rats during organogenesis at a dose of 0.16 mg/kg/day (approximately 0.02–0.06 times the Cmax in patients with cancer at the recommended human dose) caused maternal and embryofetal toxicity consisting of increased post-implantation loss, embryolethality, and fetal deaths. Decreased mean fetal birth weight associated with delays in skeletal ossification were observed at doses ≥ 0.08 mg/kg (approximately 0.02 times the Cmax at the MRHD). *In utero* exposure to cabazitaxel did not result in fetal abnormalities in rats or rabbits at exposure levels significantly lower than the expected human exposures.
If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while taking JEVTANA.

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

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

8.5 Geriatric Use
Based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of cabazitaxel between patients < 65 years (n=100) and older (n=70).
Of the 371 patients with prostate cancer treated with JEVTANA every three weeks plus prednisone, 240 patients (64.7%) were 65 years of age and over, while 70 patients (18.9%) were 75 years of age and over. No overall differences in effectiveness were observed between patients ≥ 65 years of age and younger patients. Elderly patients (≥ 65 years of age) may be more likely to experience certain adverse reactions. The incidence of neutropenia, fatigue, asthenia, pyrexia, dizziness, urinary tract infection and dehydration occurred at rates ≥ 5% higher in patients who were 65 years of age or greater compared to younger patients *[see Adverse Reactions (6.1)]*.

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

8.7 Hepatic Impairment
No dedicated hepatic impairment trial for JEVTANA has been conducted. The safety of JEVTANA has not been evaluated in patients with hepatic impairment *[see Warnings and Precautions (5.6)]*.
As cabazitaxel is extensively metabolized in the liver, hepatic impairment is likely to increase the cabazitaxel concentrations. Patients with impaired hepatic function (total bilirubin ≥ ULN, or AST and/or ALT ≥ 1.5 x ULN) were excluded from the randomized clinical trial.

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

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Revised November 2014

CAB-BPLR-SA-NOV14

(continued from SP339)

practices are assigned the task of assessing clinical benefits, toxicities, and cost, in order to select those regimens that can be appropriate in 80% to 90% of patients. This pathway can then provide a global frame of reference.

Introducing Anthem's quality initiative, the "Cancer Care Quality Program," Malin said the Web-based platform includes the prior authorization requirement as well, which can improve efficiency.

"It is important to think about value for all stakeholders. Reimbursement needs to be aligned to achieve desired outcomes while providing quality care," emphasized Malin.

PATIENT REPRESENTATION

In contrast with the 2014 annual meeting, this year ASCO invited a patient advocate to participate in the value discussion.

> *"Oncologists cannot be the gatekeepers based on cost; rather, we have the opportunity to be gatekeepers based on value."*
>
> —NEAL J. MEROPOL, MD

"Patient Priorities on Value in Treatment Choices" was the title of the talk by Beverly E. Canin, Breast Cancer Options, Inc.

Canin pointed out the need to find common ground between physicians and patients, which, she emphasized, should be based on "do no harm." She acknowledged, however, that with a disease as hard to treat as cancer, "do no harm" is a difficult goal.

Canin said that when doctors are asked about value in cancer treatment, they do not necessarily associate cost with value. In the case of patients, several of them talk about their ability to communicate with their treating physicians as a "value" concern.

She shared results from one such study which found that more than 38% of patients defined value in terms of "personal value," meaning their own personal goals and objectives, while 7% defined it in terms of "exchange" value, referring to the communication they have with their providers.

Canin emphasized the fact that the term "value" needs to be clearly defined to patients: "A clear communication is needed." Referring to a quote from Linda House, president, Cancer Support Community, Canin said there might be a disconnect between what the physician recognizes as a valuable treatment and how the patient understands it.

She aptly ended her talk with George Bernard Shaw's quote, "The problem with communication is the illusion that it has occurred." **EBO**

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A Balancing Act: Oncologist Explains the Impact of Physician Administrative Burdens

Surabhi Dangi-Garimella, PhD

ABOUT THE PRESENTER

ROBIN ZON, MD, FACP, FASCO

Dr Zon is a medical oncologist with Michiana Hematology Oncology, PC.

One of the first sessions offered at the annual meeting of the American Society of Clinical Oncology (ASCO), held at the McCormick Convention Center, Chicago, May 29-June 2, 2015, included a discussion on the growing administrative burdens in oncology practice. During the session, Robin Zon, MD, FACP, FASCO, a practicing medical oncologist from Michiana Hematology Oncology, PC, discussed the problem of the extensive amounts of time and resources utilized by physicians and the practice staff as they struggle to balance administrative burdens with clinical care.

Physicians often complain about the increasing requirements to record and maintain metrics, especially now during the transition to value-based payment models. Clinicians say the requirements siphon off vital resources from practices that are already stretched too thin.

In her talk, "Growing Concern of Administrative Burdens in Practice," Zon defined administrative burdens as "costs imposed on businesses, when complying with information obligations stemming from government regulation"—a definition provided by the Better Regulation Unit.[1]

However, said Zon, no oncology-specific database provides this information, even though many oncologists are distressed by this burden. The State Affiliate Council, an advisory group to ASCO's board of directors, through its Dashboard initiative (launched in September 2014), surveyed oncologists about how prior authorization requirements from payers are affecting their practices. A majority said the requirements demand increasing amounts of staff time, cause employee dissatisfaction, and do not seem to improve clinical outcomes.

"Will prior authorization have any effect on clinical decision making?" Zon asked.

Prior authorization is just one of the time-consuming burdens that practices face. When surveyed on the number of clinical pathways that practices have to follow—either payer-implemented or developed in-house—several responders said they had between 5 and 8 different clinical pathways in their practice, a majority of which were payer-initiated.

"Pathways are here to stay," said Zon, "but they need to be improved and they need to change over time."

> *"A 2008 survey by 2 internists found that the average doctor spends 8.7 hours per week and 1.7 hours per day on administration, which averages out to 16.6% of their working hours. This means a decrease in the number of hours that we spend in doing what we are supposed to do, which is patient care."*
>
> —ROBIN ZON, MD, FACP, FASCO

The transition from volume to value is another important change in the healthcare industry that is increasing the documentation requirements for physician practices. Thomas Gallo, MS, said at an Association of Community Cancer Centers meeting that in an attempt to collect data, which form the backbone of value-based programs, smaller practices are merging with bigger ones.

Citing a recent article in the *New England Journal of Medicine*[2] by HHS secretary Sylvia Burwell, Zon said that the government is focused on transforming our healthcare system through value-based payment goals. But pursuing these goals will all increase the physician and practice requirements for documentation.

"A 2008 survey by 2 internists found that the average doctor spends 8.7 hours per week and 1.7 hours per day on administration, which averages out to 16.6% of their working hours," said Zon. The 4720 physicians surveyed in the study spent about 168.4 million hours on administrative duties, resulting in lower career satisfaction.[3] The authors predicted that in 2014 the total cost of physician time spent on administrative duties would amount to $102 billion.[3]

"This means a decrease in the number of hours that we spend in doing what we are supposed to do, which is patient care," said Dr Zon. "I think this would result in disastrous outcomes."

"To deliver the highest quality and highest value care to patients, we need a collaboration among payers, providers, industry, patients, and employers." **EBO**

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Oncologists Inspect the Costs and Quality of Cancer Care

Surabhi Dangi-Garimella, PhD

ABOUT THE PRESENTERS

AILEEN B. CHEN, MD

Dr Chen is assistant professor of radiation oncology, Dana-Farber Cancer Institute.

RYAN DAVID NIPP, MD

Dr Nipp is clinical fellow in medicine, Dana-Farber Cancer Institute.

During the session "Health Services Research and Quality of Care" held on the second day of the American Society of Clinical Oncology meeting, held at the McCormick Convention Center, Chicago, May 29-June 2, 2015, Ryan David Nipp, MD, clinical fellow in medicine at the Dana-Farber Cancer Institute, presented results from a study evaluating the impact of an equity program intervention on the financial burden of cancer patients participating in clinical trials. The study also examined patient barriers to clinical trial participation.

"Cancer care is a big financial burden on patients," said Nipp, adding, "Clinical trial participants are uniquely susceptible to this financial toxicity."

He told the audience that the study was a collaboration, initiated in 2014, between the Cancer Care Equity Program (CCEP) at the Massachusetts General Hospital (MGH) and the Lazarex Cancer Foundation, with the goal of community outreach, patient navigation, and financial assistance. The study's purpose was to fund non-clinical expenses related to clinical trial (CT) participation, such as lodging, travel, and parking. "To determine the impact of the CCEP on CT enrollment, we compared CT enrollment in 2014 (after initiating the CCEP) with enrollment in 2012 and 2013 combined, and financial barriers were assessed through patient surveys," Nipp said.

Patients enrolled in, or being screened for, a CT were referred to CCEP by their cancer care team. These referrals, he showed, came from either an oncology provider, a nurse, a social worker, or a physician, who determines a patient's eligibility for financial assistance. Non-clinical expenses, said Nipp, include travel costs and parking. He then showed a table of demographic characteristics of trial participants; noticeably, the year 2014 had a higher proportion of patients with commercial insurance than 2012 and 2013 combined, likely the result of Medicaid expansion in the state of Massachusetts.

According to Dr Nipp, the cost associated with clinical trial participation is a major concern among cancer trial participants, and the CCEP significantly improved participation. Future studies, he said, would address financial burdens of participants and develop tools to identify individuals needing financial aid.

The results showed that trial enrollment in 2014 was significantly greater than in the previous 2 years—17% more than in 2012 and 40% greater than in 2013. Researchers noted that a greater number of minority patients enrolled in trials in 2014, and enrollment of low income patients as well as those who had to travel more than 50 miles from MGH increased in 2014. Additionally, CCEP patients were primarily female, more than 65 years of age, had metastatic disease, and had enrolled in phase 1 CTs.

The results of this study were published in *The Oncologist* just prior to ASCO.[1]

Compared with non-CCEP patients, a higher number of CCEP patients were concerned with medical costs, travel, lodging, and insurance coverage, all associated with CT participation.

Nipp concluded that the cost associated with CT participation is a major concern among cancer trial participants and that the CCEP significantly improved participation. Future studies, he said, would address financial burdens of the participants and develop tools to identify individuals needing financial aid. He encouraged stakeholders to support efforts to remove financial barriers to trial participation.

Commenting on the study, Ann H. Partridge, MD, MPH, a medical oncologist at Dana-Farber Cancer Institute and co-moderator of the session, said that although demographics did not vary much across the years being compared, the researchers had managed to hit the target. "We need to understand, though, how much the reimbursement helped patients decide on trial participation. What's the denominator—how many patients qualified for the trial, but did not participate for financial reasons and were missed?" It's essential, she pointed out, for all stakeholders who provide cancer care to rally together. "As we try to improve cancer care and reduce disparities, a robust evaluation of our efforts is necessary," Partridge concluded.

Another of the session's presentations, "How Should We Estimate Costs of Care Attributable to Cancer?", was by Aileen B. Chen, MD, assistant professor of radiation oncology at the Dana-Farber Cancer Institute.

Chen indicated that the cost of cancer care reached $100 billion worldwide in 2010-2011 and accounted for more than 5% of healthcare spending.

"However," she asked, "how do you accurately estimate these costs?" Not all of this spending is directly associated with cancer, and there are no standardized methods to estimate that. She introduced several approaches that were used in their analysis:

- Individualize costs as cancer or non-cancer, based on service item. This approach, she said is resource-intensive and demands an understanding of the fact that multiple conditions can influence cancer care costs; cancer, in turn, may affect spending on other conditions.
- Comparison groups can be matched with non-cancer patients or the cancer patients as their own control, pre-diagnosis.
- Comparison cohorts can be a demographic match: own control or demographic comorbidity match.

The study, Chen said, used SEER-Medicare data, and they calculated mean Medicare spending from 1 month prior until 11 months following diagnosis among patients older than 66 years diagnosed with lung, breast, prostate, or colorectal cancer between 2007 and 2009.

Cancer-attributable costs, she showed, were highest for all patients when using their own pre-diagnosis costs as a comparison. Cancer-attributable costs were higher among breast and prostate, but were lower among lung and colorectal patients, when using non-cancer controls, and matching by comorbidity in addition to demographic characteristics.

She pointed to a few study limitations, including the fact that their data were limited to Medicare patients with the 4 most common cancers. Additionally, she pointed to the need for using more sophisticated modeling techniques.

Chen concluded that calculating cancer-attributable costs is important in order to understand what we are spending on cancer. She acknowledged that the choice of comparison groups substantially influences the proportion of total medical costs attributed to cancer, indicating that the study observed the highest variation for prostate cancer. "Choice of reference group should be clearly delineated in the analyses of cost and value," she concluded. **EBO**

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New Oncology Clinical Trial Designs: What Works and What Doesn't?

Surabhi Dangi-Garimella, PhD

ABOUT THE PRESENTERS

RICHARD SIMON, PHD, DSC

Dr Simon is chief, Biometrics Research Branch, Division of Cancer Treatment and Diagnosis, NCI.

SUMITHRA J. MANDREKAR, PHD

Dr Mandrekar is a professor at the Mayo Clinic.

SUZANNE ELEANOR DAHLBERG, PHD

Dr Dahlberg is a research scientist at the Dana-Farber Cancer Institute.

Basket and umbrella studies as well as adaptive enrichment design strategies represent novel approaches to testing targeted therapeutics in oncology. These approaches have evolved rapidly in the last 2 to 3 years, with the objective of accelerating the drug development process so that appropriate therapies can be delivered quickly to suitable patients. At an early morning session on the third day of the annual meeting of the American Society of Clinical Oncology in Chicago, speakers discussed the nuts and bolts of these design strategies, the underlying statistical challenges, the logistical barriers with trial implementation, and the interpretation of results.

Richard Simon, PhD, DSc, who heads the Biometric Research Branch in the Division of Cancer Treatment and Diagnosis at the National Cancer Institute, discussed tools to enrich clinical trial (CT) design.

Cancer is a heterogeneous group of diseases at its primary site with respect to sensitivity to treatments, he explained. Many of these treatments are expensive and work only in a subset of patients. Standard CT design can generate a high number of false negative results, according to Simon, while trials that do yield positive results may have only a small proportion of eligible patients. Therefore, he explained, it's essential to have an elevated "number needed to treat" when designing oncology trials.

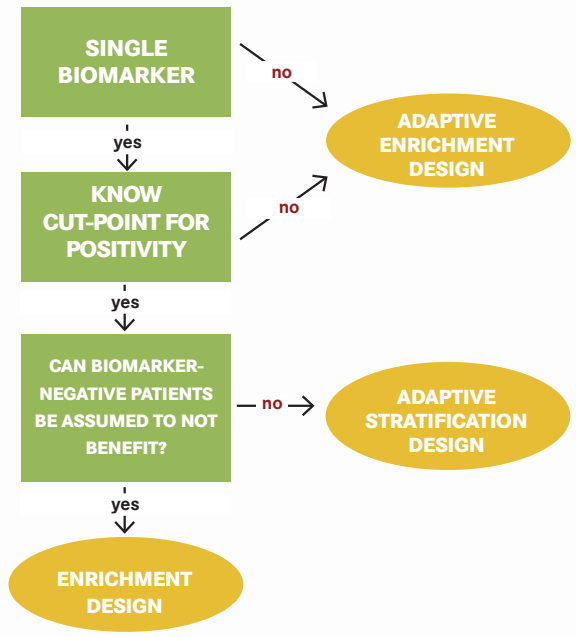
"How do we generate reliable evidence that a specific treatment will work in a particular subset of the population?" Simon asked, before describing adaptive enrichment and enrichment stratification (see **FIGURE 1**).

With the enrichment design, patients are first evaluated for biomarker expression; those who test positive are then deemed eligible for inclusion in phase 3 of the study while those who do not express the biomarker are removed. Simon indicated that this design is appropriate for phase 2 trials; if these generate biological evidence which indicates the drug is ineffective, that will point to the need to enrich the cohort being tested, and probably the need to develop a companion diagnostic as well.

Enrichment design, Simon said, has successfully been implemented in trials evaluating drugs for HER2-overexpressing breast cancers (trastuzumab), BRaf-mutated melanoma (vemurafenib), and ALK-positive lung cancer (crizotinib). Adaptive enrichment involves introducing restricted eligibility criteria at fixed interim analysis points. At the end of the trial period, a statistical significance test is performed. This design has a fixed sample size regardless of changes in eligibility, except if the trial is terminated.

The advantages of this kind of trial design, he explained, are the clarity of interpretation, and the fact that it spares the patient unnecessary exposure to the drug, particularly in cases in which the drug may not be effective. "This design helps develop a predictive biomarker, not a surrogate end point," Simon specified.

FIGURE 1. Trial Design to Enrich for the Desired Subset of a Population



In the case of a single binary biomarker, Simon said, where we do not want to assume that biomarker-negative patients will not benefit, an adaptive stratification design would be suitable. In this case, he explained, patients are randomized to receive either the new treatment or the control treatment and an intermediate end point is introduced during the trial to analyze results, such as progression-free survival.

UMBRELLA TRIALS

Umbrella studies are designed to test the impact of different drugs on different mutations in a single cancer type, and the BATTLE trial is an example of such a trial design. Sumithra J. Mandrekar, PhD, professor at the Mayo Clinic, Rochester, Minnesota, explained the rationale behind the umbrella trial design.

Mandrekar showed the umbrella trial design scheme (see **FIGURE 2**), which she said allows for a central infrastructure with multiple subtrials to test different regimens within molecularly defined patient subsets; the various subsets can share a control arm.

The trial design assumes that the biomarker and its effects on the tumor are well understood, said Mandrekar, adding that while this design has minimal or no prognostic impact, it has predictive potential. "The goals of this trial design are to facilitate patient screening and accrual, and it is quite suitable for trials evaluating low-prevalence disease," said Mandrekar, adding that the design can accelerate the speed of development and may prove useful for the rapid approval of new drugs. She then provided a list of umbrella trials for lung cancer (see **TABLE**) at various stages of drug development. A majority of these, she said, are biomarker-driven.

The primary features of umbrella trials, according to Mandrekar, are:

(continued on SP352)

TABLE. Ongoing Umbrella Trials

TRIAL	BIOMARKER-DRIVEN	DISEASE SETTING	DESIGN	DESIGN TYPE
ALCHEMIST	Yes	Adjuvant non-squamous NSCLC	Phase 3	Confirmatory
FOCUS 4	Yes	Advanced colon	Phase 2 followed by phase 3	Discovery and confirmatory
I-SPY2	No	Neo-adjuvant breast	Phase 2	Discovery
BATTLE	Yes	Recurrent NSCLC	Phase 2/3	Confirmatory
Lung-MAP	Yes	Previously treated squamous lung cancer	Phase 2/3	Confirmatory
National Lung MATRIX trial	Yes	NSCLC	Single-arm phase 2	Discovery

NSCLC indicates non-small cell lung cancer.

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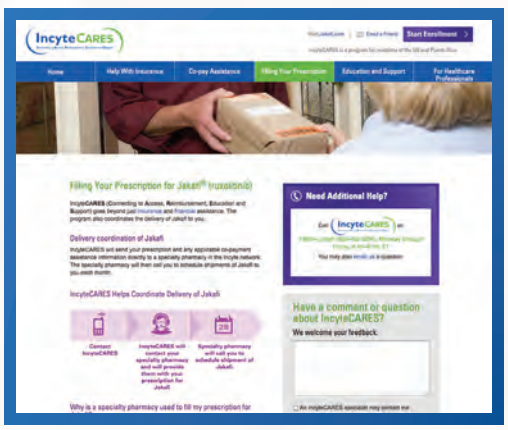

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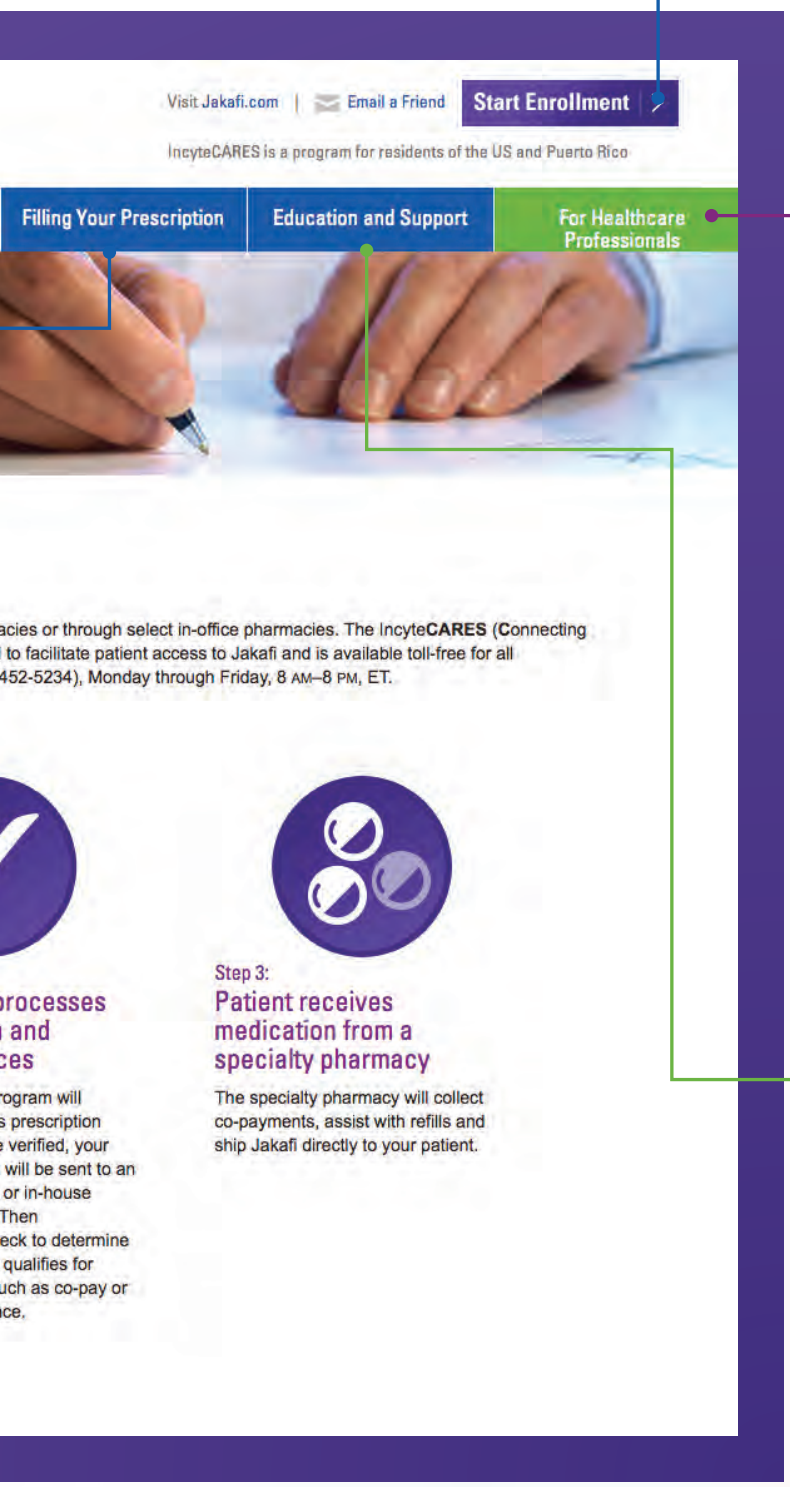

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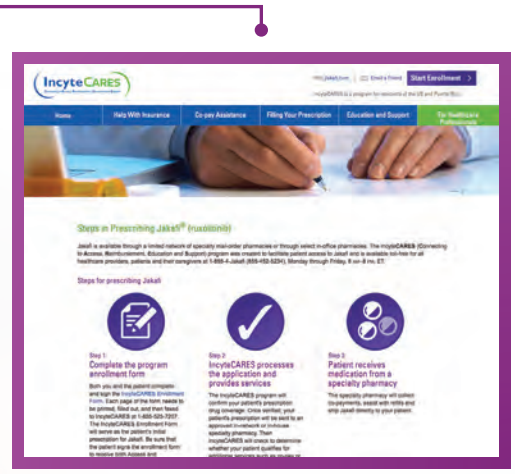

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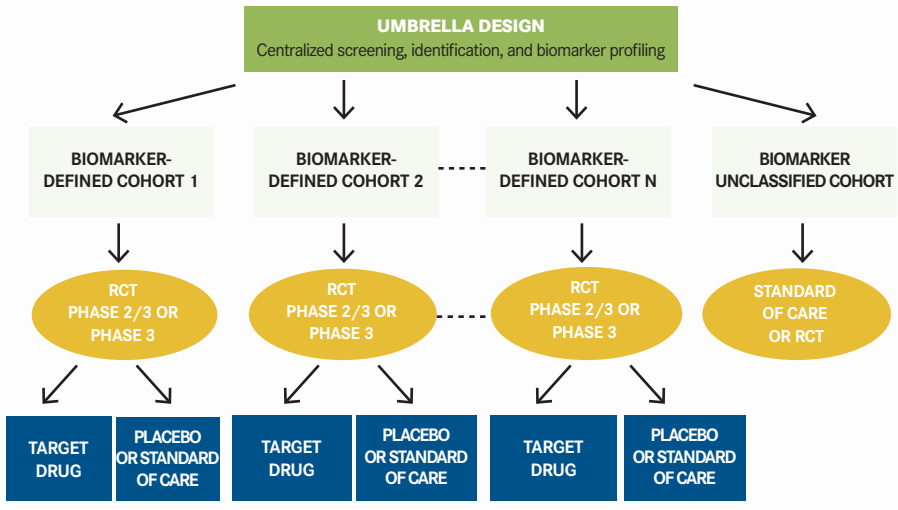
FIGURE 2. Umbrella Trial Design



RCT indicates randomized control trial.

- The inclusion of multiple treatments and multiple biomarkers within the same protocol
- A design that allows for randomized comparisons
- A design that can have flexible biomarker cohorts
- A design that can add/drop biomarker subgroups

She did point out several logistical challenges associated with implementing a large-scale endeavor like an umbrella trial. These include acquiring patient consent and patient enrollment and tracking—"It takes a huge team effort."

BASKET TRIALS

Basket studies are designed to test the effect of a single drug on a single mutation in a variety of cancer types. They provide a unique way of merging the traditional CT design with rapidly evolving genomic data that facilitate the molecular classification of tumors. During her talk, "Basket Trial Designs: Identifying the Exceptional Responders," Suzanne Eleanor Dahlberg, PhD, research scientist at the Dana-Farber Cancer Institute, introduced this other novel trial design.

Basket trials aim to assess targeted therapeutics that have a dramatic clinical impact, with a focus on biological drivers of response. "So patients who harbor a specific mutation or over-express a particular protein, targeting that particular abnormal signaling pathway could yield a dramatic improvement in patient response," Dahlberg said.

> *"The advantages of [the enrichment design] are the clarity of interpretation, and the fact that it spares the patient unnecessary exposure to the drug, particularly in cases in which the drug may not be effective."*
>
> —RICHARD SIMON, PHD, DSC

She noted that although a basket trial is an efficient way to screen multiple drugs across many patient populations, it is not a formal statistical design. Rather, it is designed based on a genetic abnormality in the patient's tumor.

Emphasizing that the trial design can greatly improve trial efficiency, Dahlberg said that basket trials can screen multiple drugs across many cancer types. While genomic variability exists across multiple tumor types, not every mutation is necessarily actionable across all of them. She believes the basket design provides a strong rationale to pair a drug with a validated biomarker in a specific tumor.

Noting that these are discovery-phase trials, Dahlberg explained that they can be used for drug development in rare cancers. "The trials can be conducted across multiple institutions, rely on sample availability, and need a sufficient number of drugs that can target multiple tumor types."

Citing NCI-MATCH (Molecular Analysis for Therapy Choice Program) as an example of a basket trial design,[1] Dahlberg said that it is a collaboration between the ECOG-ACRIN Cancer Research Group and the National Cancer Institute. The trial, which at press time was scheduled to initiate enrollment in July, will assign treatment based on "actionable mutations" in the tumor. Each of the 10 arms in the trial will enroll adults with advanced solid tumors and lymphomas who are refractory to standard therapy.[1]

Several criteria influence the drug selection process, she said. The molecules could be FDA-approved for a predictive indication, or have a biomarker; investigational drugs can be included if they have predictive molecular value.

Dahlberg concluded: "Basket design can accelerate the delivery of the right treatment to a patient, but it requires that strong biomarkers be associated with the drug. Additionally, heterogeneity in response across disease types is a primary consideration, and clonal variation has to be adapted during trial design." **EBO**

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Largest-Ever Precision Medicine Oncology Trial Ready for Launch

Anita T. Shaffer

A landmark clinical trial that will channel patients into treatment arms based on molecular abnormalities rather than cancer type aims to simultaneously test the efficacy of more than 20 drugs, in an ambitious National Cancer Institute (NCI) plan to further propel oncology drug discovery into the precision medicine era.

Starting in July, the NCI-MATCH trial will seek to recruit 1000 adults 18 years or older with progressive advanced solid tumors and lymphomas that are either refractory to standard therapy or for which there is no standard therapy. Participants will be assigned to small phase 2 trials based on molecular tumor profiling of specimens from biopsies conducted at the time of study entry.

The trial is "a critical and leading part" of the nation's precision medicine initiative, Clifford A. Hudis, MD, FACP, said during a press briefing at the 2015 annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago, where NCI-MATCH and other innovative research projects were detailed.

"In oncology, we've embraced this idea for years," said Hudis, a past president of ASCO and a breast cancer specialist at Memorial Sloan Kettering Cancer Center. "The initiatives that we're discussing today reflect not a new initiative, but an expansion of an ongoing dream that we have been pursuing."

"This is the largest and most rigorous precision oncology trial that's ever been attempted," said James H. Doroshow, MD, the NCI's deputy director.

The NCI has made an internal commitment to fully fund the study, according to Doroshow, independent of the discussions now under way in Congress over the $215-million appropriation the Obama administration has proposed for the precision medicine initiatives in cancer and other diseases. He added that it probably would cost $30 million to $40 million for the first stages of NCI-MATCH, and that the budget could expand by 15% to 20% as more drugs are added to the list of agents tested and additional substudies are conducted. The NCI will pay for biopsies and laboratory sequencing tests, officials indicated.

The project will launch with an initial list of 10 substudies, in which both previously approved drugs and investigational agents will be evaluated. Barbara A. Conley, MD, NCI study co-chair, said plans call for the trial to ramp up to more than 20 treatment arms within months of its launch.

FIRST BATCH OF DRUGS IDENTIFIED

Here is the list of drugs that Conley identified for the first batch of studies and the molecular targets with which they are paired:

- Crizotinib—Separate studies in *ALK* rearrangements and *ROS1* translocations
- Dabrafenib and trametinib—*BRAF V600E* or *V600K* mutations
- Trametinib—*BRAF* fusions or *non-V600E*, *non-V600K BRAF* mutations
- Afatinib—Separate studies in *EGFR* and *HER2* activating mutations
- AZD9291—*EGFR T790M* and rare *EGFR* activating mutations
- T-DM1—*HER2* amplifications
- VS-6063—*NF2* loss
- Sunitinib—*cKIT* mutations

The FDA has approved 6 of the drugs

(continued on SP354)

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

Session 3: The Future of Immuno-oncology

- Are We Close to the Big "C": Cure?
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- ***Panel:*** The Role of PBMs in Managing High-Cost Treatment Options

Session 4: Innovations for Patient-Centered Care

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- Payment Models in Oncology Care at the Patient Level
- ***Panel:*** Navigating the Conflict of Personalized Medicine vs Population Management

Session 5: Accountable Care in Oncology

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

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(continued from SP352)

on the list: crizotinib (Xalkori), dabrafenib (Tafinlar), trametinib (Mekinist), afatinib (Gilotrif), T-DM1 (Kadcyla), and sunitinib (Sutent).

AZD9291, a third-generation EGFR inhibitor, is being evaluated under the FDA's breakthrough therapy program for patients with non-small cell lung cancer (NSCLC) whose tumors harbor the T790M resistance mutation. VS-6063, also called defactinib, is a small-molecule FAK inhibitor in phase 1/2 testing in mesothelioma, NSCLC, and ovarian cancer.

In order to enroll enough patients with mutations to allow a treatment match, organizers anticipate that 3000 patients will have to be screened. The goal is to enroll approximately 30 patients in each study.

An essential facet of the trial is the need to employ accurate assays to identify patients with the appropriate molecular features of their tumor, Conley said. Organizers have set up a network expected to provide molecular profiling results within 14 days or less. Genomic testing will be performed using the Ion Torrent Personal Genome Machine System's custom panel of 143 genes, which in turn harbor more than 4000 variants.

For every trial, the primary end point will be overall response. Secondary end points include 6-month progression-free survival, time to progression, toxicity, and biomarker status.

The NCI-MATCH trial marks the next step in the agency's efforts to harness the promise of precision medicine in oncology, starting with The Cancer Genome Atlas project to characterize genetic abnormalities in a range of cancer types, Doroshow said. Describing the planning and ultimately the conduct of NCI-MATCH as a national effort, he said, "It has taken an absolute village to build this trial. Hundreds of people supported the launch of the trial so far. Ultimately, it will take thousands of investigators to execute this study."

The ECOG-ACRIN Cancer Research Group, which was formed 3 years ago through the merger of 2 oncology research organizations, is partnering with the NCI to plan and carry out the study at 2400 sites nationwide.

One of the army of investigators who will be involved in NCI-MATCH is Juneko Grilley-Olson, MD, an assistant professor at the University of North Carolina Lineberger Comprehensive Cancer Center who specializes in thoracic, bone, and soft tissue oncology. She will help lead a substudy involving the investigational PI3K inhibitor GDC-0032, also called taselisib, which is expected to be studied in the second wave of trials that start as NCI-MATCH expands. Patients whose tumors harbor a *PIK-3CA* mutation without a *KRAS* mutation and without *PTEN* loss are candidates for the study, Grilley-Olson said in an interview.

Grilley-Olson noted that NCI-MATCH organizers are hoping that at least 25% of the patients who enroll in studies have rare cancers. "Those are tumors that often don't have dedicated trials," she said. "In the PI3 kinase arm we would be looking to enrich it for rarer tumors that have not been as extensively studied. With tumors such as breast cancer or lung cancer, we probably wouldn't learn as much additional information in a 30-patient cohort, because they have been studied in trials with hundreds and hundreds of people [in those cancers]." **EBO**

ABOUT THE PRESENTERS

BARBARA A. CONLEY, MD

Dr Conley is associate director of the Cancer Diagnosis Program, National Cancer Institute.

CLIFFORD A. HUDIS, MD, FACP

Dr Hudis is past president of ASCO and medical oncologist at the Memorial Sloan Kettering Cancer Center.

POSTER ROUND UP

Phase 3 RECOURSE Trial Holds Promise for Colorectal Cancer

Surabhi Dangi-Garimella, PhD

Colorectal cancer, with a 5-year survival of 64.9%, is projected to result in 8.4% of all cancer deaths in 2015.[1] The 5-year survival for patients with localized disease is even better, at 90.1%. Standard of care for patients with metastatic colorectal cancer (mCRC) has evolved over the years. Treatment, which was restricted to the thymidylate synthase inhibitor 5-fluorouracil (5-FU) in early years, now includes folinic acid along with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX). Additionally, presence of a wild-type *RAS* would mean inclusion of either a vascular endothelial growth factor inhibitor or an epidermal growth factor inhibitor.[2,3]

A poster presented at the annual meeting of the American Society of Clinical Oncology, results of which were also published in the *New England Journal of Medicine*,[3] showed phase 3 data from the RECOURSE trial after evaluating specific geographic subgroups: the United States, Europe, and Japan.[4] The trial evaluated the oral drug TAS-102, a combination of trifluridine and tipiracil hydrochloride, designed to maintain appropriate plasma levels of the active drug trifluridine. The phase 2 study of TAS-102, conducted in 169 Japanese patients with metastatic colorectal cancer who were refractory to 5-FU, irinotecan, and oxaliplatin, improved median overall survival (OS) from 6.6 months in the placebo group to 9.0 months in the treated group.

The phase 3 study extended the trial to a global population of 768 patients with mCRC who were either refractory to antitumor agents or had experienced significant adverse events with the treatment. Of the 768 patients, 99 in the United States, 403 in the European Union, and 266 in Japan were randomized to receive TAS-102 or placebo.

As shown in the **TABLE**, OS improved in mCRC patients in the TAS-102 arm across all 3 geographical subgroups that were evaluated. Overall, the incidence of adverse events (AEs), serious AEs, and hospitalizations was similar across the subpopulations treated with TAS-102.

The authors concluded that TAS-102 had an acceptable safety profile, and offered OS and progression-free survival benefits to mCRC patients across the geographically divided cohorts. **EBO**

TABLE. Overall Survival (OS), Months: Geographic Comparison

	UNITED STATES		EUROPEAN UNION		JAPAN	
	TAS-102	Placebo	TAS-102	Placebo	TAS-102	Placebo
Median OS	6.5	4.3	6.8	4.9	7.8	6.7

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Real-World and Phase 1 Safety Studies of Immuno-Oncology Agents in NSCLC and Glioblastoma

Surabhi Dangi-Garimella, PhD

SAFETY STUDY OF NIVOLUMAB IN COMMUNITY ONCOLOGY CENTERS

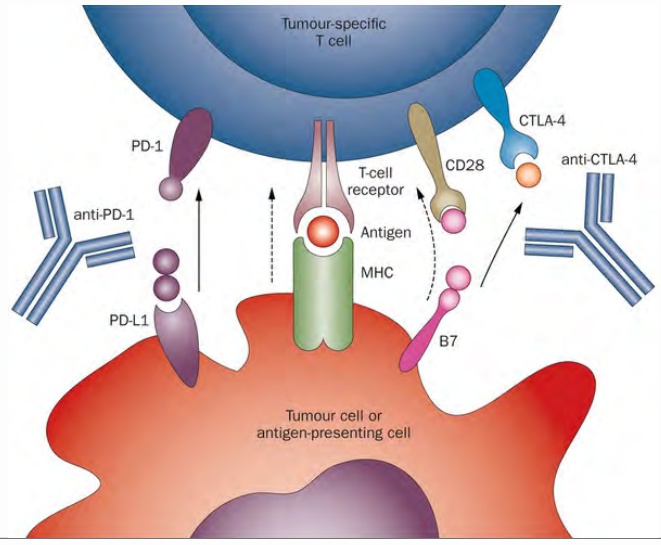
The fully humanized PD-1 inhibitor nivolumab is currently approved to treat melanoma patients who have progressed on ipilimumab and patients with squamous non-small cell lung cancer (NSCLC) who have progressed on platinum-based chemotherapy.

A poster presented on the second day of the annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago presented results from a phase 3/4b safety study of nivolumab in 824 previously treated NSCLC patients, primarily conducted in community-based oncology centers. A majority (72%) of patients had the non-squamous form of the disease; the rest (28%) had squamous NSCLC. Patients received intravenous nivolumab (3 mg/kg for 60 min) once every 2 weeks, either until progressive disease or unacceptable toxicity (cohort A) or for 1 year with the possibility of retreatment upon disease progression (cohort B). The primary objective was to estimate the incidence of high-grade (3-5) select treatment-related adverse events (AEs). The trial also explored efficacy and evaluated objective response rate, progression-free survival, and overall survival (OS).

Results. At week 9, of the 531 evaluable patients, 12% demonstrated a partial response per RECIST v1.1, with no complete response observed. The authors claim that the efficacy follow-up period was relatively short, with an average on-study time for these data of only about 10.4 weeks. Treatment-related select AEs (SAEs) observed included cardiac disorders, endocrine disorders, gastrointestinal (GI) disorders, general disorders, hepatic disorders, musculoskeletal disorders, nervous system disorders, skin disorders, and respiratory and metabolic disorders. A majority of patients presented with skin disorders and GI disorders.

Conclusions. The authors conclude that safety and tolerability are consistent with prior nivolumab experience, and no new safety signals have been identified in this trial. Drug-related toxicities are manageable in a community practice setting using previously developed management algorithms. The frequency of treatment-related SAEs and SAEs of interest were similar between patients with performance status (PS) 0 to 1 and those with PS 2. Early data from this large multicenter trial suggest that patients with pretreated advanced NSCLC benefit from nivolumab therapy, regardless of histology type, performance status, *EGFR/ALK* mutation status, number of prior therapies, or smoking status.

FIGURE. Mechanism of Action of Ipilimumab (Anti-CTLA-4) and Nivolumab (Anti-PD-1)



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CHECKMATE-143 EVALUATES SAFETY AND EFFICACY OF NIVOLUMAB, ALONE OR IN COMBINATION WITH IPLILIMUMAB IN GLIOBLASTOMA

Glioblastoma (GBM), a malignant brain cancer in adults, continues to present a grim prognosis despite current first-line therapies. Median OS with first-line treatment of surgery, radiotherapy, and temozolomide is 15 to 17 months; the 3-year survival rate is a dismal 10% to 15%, and the 5-year survival is even lower, at 1% to 5%. Treatments for relapsed patients have limited success and are clinically aggressive for the patient, resulting in poor quality of life.

The rationale behind this CHECKMATE-143 trial, according to the authors, is the reduced risk of gliomas and longer survival observed in individuals with elevated immunoglobulin E levels. Since inhibition of PD-1 and CTLA-4 has yielded impressive results in melanoma and in lung cancer, the authors evaluated the combination of nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor) in patients with recurrent glioblastoma. Preclinical studies with nivolumab prolonged survival in a glioblastoma mouse model, and combining both agents increased tumor infiltration of T-effector cells.

The abstract, presented on the third day of the annual meeting of ASCO in Chicago, included safety, tolerability, and preliminary efficacy results from phase 1 of the trial. Patients were randomized 1:1 to receive nivolumab 3 mg/kg once every 2 weeks or nivolumab 1 mg/kg + ipilimumab 3 mg/kg once every 3 weeks for 4 doses followed by nivolumab 3 mg/kg once every 2 weeks. The primary end points were safety and tolerability.

Eligibility criteria were:

- First recurrence of grade IV primary glioblastoma
- No prior bevacizumab treatment
- Interval of at least 12 weeks after end of prior radiotherapy and a confirmation of recurrent tumor or MRI-confirmation of enhancement outside of radiotherapy treatment field
- Karnofsky performance status ≥70.

Exclusion criteria were:

- >1 glioblastoma recurrence
- Presence of extracranial metastatic or leptomeningeal disease
- Known or suspected autoimmune disease
- Previous treatment with vascular endothelial growth factor or anti-angiogenic agents
- Cardiovascular disease.

Results. The study included 20 patients, 10 in each arm, with similar demographic and disease characteristics. Assessments were made after the last patient in each arm had completed 4 doses of the study medication, and AEs were collected for at least a 100 days following the last dose. Of the 20 patients, 14 (6 in the nivolumab-alone arm) died. The authors did not report any unexpected side effects, and safety profiles mirrored other tumor types. Most common treatment-related AEs included diarrhea, fatigue, and increased lipase. Treatment-related serious AEs were observed in 2 and 7 patients in the monotherapy and the combination arms, respectively. The combination regimen resulted in more treatment-related discontinuation (4/10) compared with none on the monotherapy arm, after the first 4 doses.

Preliminary efficacy evaluation from this trial showed a partial response in 1 patient receiving monotherapy and stable disease in 4 patients in each treatment arm.

Conclusions. The authors concluded that nivolumab monotherapy was well tolerated in this recurrent glioblastoma population, with no treatment-related grade 3 to 4 AEs observed and no treatment-related discontinuations within the first 4 doses of treatment. The combination of ipilimumab and nivolumab, on the other hand, was associated with a higher incidence of treatment-related grade 3 (n = 7/10) and grade 4 AEs (n = 2/10). Treatment-related effects observed on histopathology and neuroimaging suggest biologic activity at the tumor site. The safety profile and preliminary clinical activity of nivolumab monotherapy observed in this phase 1 study led to the initiation of phase 3 of CHECKMATE-143 to assess efficacy compared with bevacizumab in patients with recurrent glioblastoma. **EBO**

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Will Specialty Oncology Products Follow the Sovaldi Way?

Surabhi Dangi-Garimella, PhD

The approval of Sovaldi in 2014 to treat hepatitis C revolutionized the disease treatment landscape. Following the subsequent cost debates and widespread criticism of the 12-week, $84,000 Sovaldi regimen, Medicaid and some other health plans took a more restrictive approach, limiting access to the drug to patients with more advanced disease.[1] With the launch of Gilead's second-generation drug Harvoni, and then Abbvie's Viekira Pak, formulary wars followed, with the pharmacy benefit manager (PBM) Express Scripts giving precedence to Viekira Pak over Sovaldi.[2]

Some of the new oral oncology drugs—many of which are molecularly targeted precision medicine treatments—also fall under the heading of specialty pharmaceuticals and are quite expensive. To discuss the challenges associated with managing and paying for some of these agents, *The American Journal of Managed Care* invited a group of healthcare experts to participate in the Oncology Stakeholders Summit, Spring 2015 Peer Exchange. Bruce Feinberg, DO, vice president and chief medical officer of Cardinal Health Specialty Solutions, moderated the panel that consisted of Scott Gottlieb, MD, resident fellow at the American Enterprise Institute; Brian Kiss, MD, vice president of healthcare transformation at Blue Cross Blue Shield of Florida; Michael Kolodziej, MD, national medical director for oncology strategy at Aetna; and Ted Okon, MBA, executive director of Community Oncology Alliance (COA).

While precision medicine has tremendous potential and expands patient options, the growth in the field of oral therapeutics will significantly affect payers, said Feinberg, because of the arbitrary separation that exists between pharmacy benefit and medical benefit. Feinberg explained that oral therapeutics will have a huge impact on physician clinics where chemotherapeutic infusions were traditionally administered, because not all clinics have the ability to dispense these medications through an onsite pharmacy, and in many cases state laws prohibit it. He also questioned whether oral treatments will be effective in maintaining patient-centeredness.

Patients often mistake oral therapy for a cheaper alternative to chemotherapy, said Okon. He agreed with Feinberg that with oral medications accounting for 25% to 35% of the oncology pipeline, we have a new situation to which everyone must adapt. Okon went on to explain the real-world problems with oral therapeutics, especially concerning treatment adherence. While the provider retains control with infusion treatments, with oral drugs, the onus lies with the patient. "We've done a lot of research at COA on this, and basically, it's actually tied to cost," he said. According to Okon, studies have shown that irrespective of cost, 10% of patients don't fill even the first prescription, which complicates clinical and payer decisions if the treatment fails. Specialty pharmacies have picked up on managing this uncertain aspect of oral oncolytics, Okon thinks, which further releases the control clinical practice has traditionally had over treatment. "And we have not even touched upon the reimbursement issues or the structural issues that are influenced within the community practice."

THE PAYER STRATEGY

Feinberg turned to the payers in the room, asking each to explain the strategy for medication therapy management, adherence, compliance, and persistence, and how these expensive medications impact the overall payer budget.

Kiss said that payers have found a way out: negotiating price deals with vendors. But these channels may not be accessible to a clinical oncologist, he said. "So you have a drug that's $1000, which may be the patient's out-of-pocket cost. They take the prescription to their Walgreens. And you know Walgreens can get the drug in 48 hours and still do it, but [now] instead of being $1000, it may be $1400." These variables have resulted in an increasing shift of cost burden to the patient, according to Kiss. Another complication is that patients have the option of receiving these oral oncology drugs by mail order; if they cannot tolerate the side effects of the drug, they might stop taking them in a few days, "Which can result in huge wastage because now they have the rest of the month's supply in their medicine cabinet." Both Feinberg and Kiss noted that this problem is not confined to oncology; already, we are seeing a spillover into rheumatology and other therapeutic areas where novel oral therapeutics are being developed.

Kolodziej had a slightly different perspective to offer. The specialty pharmacy infrastructure created by PBMs is adept at handling the complicated procedure of prior authorization, diverse benefit designs, coinsurance, co-payments, and so on, he said. He explained that while a tiered system increases the efficacy of handling high-volume drugs and helps with cost negotiations, "Specialty medications don't really fit those rules. Fracturing the tight association between specialty pharmacies and the PBMs and the relationships that payers have with PBMs, has potential consequences and it's not something that will be done," Kolodziej explained.

Gottlieb seemed to disagree with this argument presented by Kolodziej and asked why payers cannot independently contract for specialty drugs with the vendor. While Kolodziej conceded that this is a possibility, he warned of a huge pushback from the PBMs.

> *"Fracturing the tight association between specialty pharmacies and the PBMs and the relationships that payers have with PBMs, has potential consequences and it's not something that will be done."*
>
> —MICHAEL KOLODZIEJ, MD

When asked to prescribe a solution, Kolodziej said that defining the problem at hand is extremely important. "Are we trying to fix prior authorization, are we trying to fix co-payment, or are we trying to fix adherence?" He would prefer to see a practice implement procedural changes to improve patient adherence, rather than reengineer the existing system: "The real impediments to dispensing these drugs and getting a patient to adhere are related to other defects in the system."

Okon agreed, adding that at a recent COA board meeting, standards were proposed for community oncology practices that operate retail pharmacies in states where it's permitted. COA, he said, announced the formation of the Community Oncology Pharmacy Association (COPA).[3] Among other things, COPA's advisory board has issued the following agenda:

- Developing national quality measures for practice-based dispensing and retail pharmacies in conjunction with accreditation recognition.
- Conducting and publishing an independent analysis documenting the quality, compliance, and low costs of patients being treated in dispensing and retail pharmacies within integrated community oncology practices versus disconnected specialty pharmacy providers.
- Establishing a closed listserv enabling information sharing among COPA members on best practices.
- Creating a website with resources available to practices that have a dispensing or retail pharmacy as well as those looking for resources to assist in establishing a pharmacy.[4]

Kolodziej said that while split-fills can partially address the likely problem of drug wastage, an enhanced care model, with an intervention offered at the physician's office, would be an ideal route to follow. He went on to cite a study conducted in patients with chronic myelogenous leukemia who were taking tyrosine kinase inhibitors. The study found that increasing the patient's responsibility for self-care increased noncompliance from 12% to 17%. For Kolodziej, the baseline value of nonadherence was intriguing. "Why were 12% of the patients not taking a drug that can cure and which has few side effects?" He believes there are several nuances to the adherence problem, and site of care cannot address all of them. Okon added that tiered formularies with a high co-payment can also influence adherence.

DO ONCOLOGISTS INFLUENCE COST?

Kiss introduced the subject of the buy-and-bill practice, in which clinics purchase and stock their own medications and then charge the health plans, including a markup. In his opinion, payment reform should emphasize changing how community oncologists are compensated. "They should be paid for their cognitive and technical skills and not have to depend on drug profits, even if they are the pharmacy."

Kolodziej defended buy-and-bill, pointing out that it's a system that evolved as care migrated from the hospital to the community setting. But the community practices could not translate the structural requirements needed to deliver this care, and the buy-and-bill practice is a product of this adaptation. He said that while margins are necessary for supporting the infrastructural needs of a community practice, he believes—and studies have shown—that "Doctors do not generally make therapeutic decisions based on margin. I would like a system that could transition from that model that is perceived to be conflicted, to a model that is more rationally based on performance, outcome, services; but the math is very, very difficult."

Kiss added that while the system

wasn't really being abused, it called for reform while being fair with compensating oncologists. "Do we allow [oncologists] to share in this part of the drug [cost] or is this an opportunity to migrate the payment system? And I think that's the only point."

Gottlieb thinks that the perception within CMS that doctors are conflicted has resulted in additional government regulation on decision making, with the implementation of more Part B rules around the provision of oncology products. "That's unfortunate, and it's another thing to think about as we contemplate a different system," he said.

Okon argued that if drug incentives were a profitable option, we wouldn't see as many cancer clinics shutting down or migrating over to health systems. Citing studies conducted by Avalere and the Milliman Group, he said, "We have more and more data that present a very interesting picture about what physicians do or don't do or think about in terms of the incentive and where it really exists, which is on the hospital side."

EASING COSTS IN THE ONCOLOGY MARKET

Feinberg then transitioned the discussion to specifically address the cost of these specialty medications. With competition, rebates, and payer relations, a pricing shift was observed with Sovaldi; would this be reflected in oncology? "Who would take the lead in this shifting landscape, if it does happen: payers or PBMs?"

Gottlieb summarized the case of the hepatitis C regimens, saying that com-

Experts discuss the ideal time to initiate cost discussions in oncology.

petition drove down the prices. His suggestion is to allow second-in-class drugs to enter the market as efficiently as the first-in-class, especially with respect to regulatory procedures.

The panelists agreed that the sheer number of patients—a majority of whom are baby boomers—was the primary reason for price concern with the hepatitis C medications, in addition to the high price. Gottlieb noted that while newer drugs in the pipeline may not necessarily treat a large number of patients, many of them—especially gene therapy–based approaches—are very expensive. "So I think that probably requires us to have a discussion about different ways to finance these things and to potentially amortize these costs."

Kolodziej believes that competition will definitely drive down the cost of the novel immuno-oncology agents, and that if all the PD-1 and PD-L1 agents are treated as a single drug class, the market could then regulate the price of these drugs.

Okon and Gottlieb agreed that a free market approach without price controls is called for to avoid what happened with Sovaldi. Gottlieb suggested that drug manufacturers adopt competitive models and options provided by PBMs.

Kiss, however, highlighted an extremely important point: that drugs account for only 20% to 25% of fixed oncology healthcare spending. He said it's important to understand how this 20% to 25% of drug cost influences the remaining 75% of healthcare cost.

So whose opinion matters the most with cost, and how early should these stakeholder discussions be initiated?

"I think [drug manufacturers] are making more of a concerted effort to engage the payers much earlier in discussions around their pipeline and what information the payers are going to find meaningful to make coverage decisions," said Gottlieb. But in his opinion, drug developers should also be in conversation with consolidated delivery systems that take capitated risks—in the future, "They are going to become much more active in steering these decisions." **EBO**

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To watch the discussion online, visit **http://bit.ly/1G5xPkt**.

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Palliative Care in Cancer: When Does the Discussion Begin?

Surabhi Dangi-Garimella, PhD

Palliative care discussions are now starting earlier in oncology, as patients and providers realize that palliative care does not equal end-of-life care. A team effort, palliative care requires communication among providers, caregivers, the patient, and the family in order to achieve the patient's goals for pain and symptom management alongside curative therapy. However, not all clinics or healthcare systems have integrated palliative care into their care plan. While a palliative care physician and nurse might be considered a vital part of the cancer care team at one clinic, a conversation on pain management or end-of-life care may not even occur at others.

A study published 5 years ago in *Health Affairs* found that nearly one-fourth of Medicare expenditures were made to beneficiaries in their last year of life.[1] Could the integration of palliative care save on these costs? And then there's the issue of reimbursement. How do you reimburse for the time a palliation consultant spends with the patient?

The American Journal of Managed Care brought together a panel of healthcare experts to discuss some of these questions and challenges during the Oncology Stakeholders Summit, Spring 2015 Peer Exchange. Moderator Bruce Feinberg, DO, vice president and chief medical officer of Cardinal Health Specialty Solutions, was joined by Scott Gottlieb, MD, resident fellow at the American Enterprise Institute; Brian Kiss, MD, vice president of Healthcare Transformation at Blue Cross Blue Shield of Florida; Michael Kolodziej, MD, national medical director for oncology strategy at Aetna; and Ted Okon, MBA, executive director of Community Oncology Alliance (COA).

Feinberg broached the topic of palliative care by narrating the story of a friend whose 93-year-old aunt had a procedure-associated complication and ended up on a ventilator. When the nephew reached the hospital, he was asked how he'd like to continue treatment and handed a list of everything that "do not resuscitate" (DNR) entails. Following an unproductive conversation with the resident physician, a palliative care specialist was called in, which helped ease the process. "Statistics show that only 50% of eligible patients end up in hospice care, with an average length of stay of just 7 days," said Feinberg, asking, where should the conversation start?

"Integrating palliative care into mainstream cancer care is inevitable with increasing consolidation in healthcare." —Scott Gottieb, MD

Palliative care discussions need to start well before the end stage of disease or before the patient has intractable pain, according to Kiss. End-of-life care discussions can be initiated in patients who are at an early stage of their disease or even in patients who have enrolled in primary care, he said.

"This is by far the hardest part of the job of being an oncologist," said Kolodziej. In his opinion, this conflicts with what oncologists are primarily trained to do, and necessitates a systemic change. He also drew attention to the slough of definitions and terms that could confuse anyone trying to come

to a decision, including advanced care planning, end-of-life care, and hospice care. Kolodziej believes in leading by example, though, and said that he tells his patients: "I have a healthcare proxy. I have a will. I have made my goals and what I'm interested in known to those I love. I would strongly recommend that we have that discussion and we have it with your family."

Feinberg suggested that oncologists might push back on adding another specialist to their team, which may already include a radiation, surgical, and medical oncologist. Okon responded by saying that the entire practice, not just the oncologist, would have to adapt and the changes would have to be built into the "fabric of the practice," echoing Kolodziej. He added that this change would loop back to the patient, ensuring a more patient-centered approach that could enhance the patient's quality of life and treatment goals.

Kolodziej believes in leading by example, and said that he tells his patients: "I have a healthcare proxy. I have a will. I have made my goals and what I'm interested in known to those I love. I would strongly recommend that we have that discussion and we have it with your family."

Feinberg spoke about certain restrictions that CMS has incorporated with reimbursement benefit design, such as the fact that a patient in hospice care cannot get a blood transfusion. This ties the provider's hands in terms of care delivery, especially for patients with advanced disease. "[The system] has these black-and-white determinants of when things can be done," he said.

Gottlieb agreed that CMS is very rigid with hospice care, especially since the length of stay in hospice has been steadily increasing. In the subsequent struggle for balance, reimbursement changes are made that don't work in favor of hospice care providers, he said. He agrees that DNR conversations and decisions should be made early, at the outpatient stage, not when the patient is hospitalized and in need of advanced care.

"If you think about why patients 'cost' so much at end of life, it's because they're receiving acute care in the hospital," said Kolodziej, emphasizing that acute inpatient care is the cost driver, in addition to unnecessary chemotherapy administration, and a system that is not adept at managing symptom burden. Do we have a solution, then? Generating a reimbursement code for when a doctor discusses advanced care planning (ACP) with the patient is not going to change the situation, said Kolodziej. "It's a process, not a 15-minute time slot where you discuss ACP."

He went on to explain that the current healthcare system needs a makeover with respect to managing patients with advanced disease. Describing Aetna's Compassionate Care program,[2] Kolodziej said that specially trained nurses are assigned to address patient concerns and to help them plan and achieve their treatment goals. "The goal is not to enroll them in hospice, and the goal is not to get a DNR. The goal is to have the discussion," not necessarily with a palliative care physician, because we do not have enough of them, he said.

Kiss said that some of Blue Cross Blue Shield's cancer accountable care organizations are integrating a palliative care physician and even a palliative care nurse as a part of team-based care. This integration ensures that the patient does not have to endure a change of care from treatment to palliation, and he finds this encouraging.

Gottlieb thinks the integration of palliative care into mainstream cancer care is inevitable given the increasing consolidation in healthcare and practices taking capitated risks. "The incentives on the part of the providers are going to change, too, and that will also impact these decisions." **EBO**

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To watch the discussion online, visit **http://bit.ly/1SJM1ZH**.

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