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ASCO ANNUAL MEETING | JUNE 3-7, 2016, CHICAGO, ILLINOIS

EXCLUSIVE COVERAGE!

ASCO ANNUAL MEETING
COLLECTIVE WISDOM
2016
THE FUTURE OF PATIENT-CENTERED CARE AND RESEARCH

HIGHLIGHTS FROM THE MEETING

AJMC®
Managed Markets Network®

NEW DATA: IMBRUVICA® EXTENDED OVERALL SURVIVAL VS CHLORAMBUCIL IN FRONTLINE CLL/SLL

CLL
SLL

IMBRUVICA® is a once-daily oral therapy indicated for

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)[1]
- CLL/SLL with 17p deletion[1]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including 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 and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and postsurgery depending upon the type of surgery and the risk of bleeding.

Infections - Fatal and nonfatal infections have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA®. Evaluate patients for fever and infections and treat appropriately.

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%) based on laboratory measurements occurred in patients treated with single agent 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, hypertension, 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. Atrial fibrillation should be managed appropriately and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension - Hypertension (range, 6% to 17%) has occurred in patients treated with IMBRUVICA® with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new-onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®. Adjust existing antihypertensive medications and/or initiate antihypertensive treatment as appropriate.

Second Primary Malignancies - Other malignancies (range, 5% to 16%) including non-skin carcinomas (range, 1% to 4%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4% to 13%).

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

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RESONATE™-2 was a multicenter, randomized 1:1, open-label, Phase 3 trial of IMBRUVICA® vs chlorambucil (N=269) in frontline CLL/SLL patients ≥65 years[1]

EXTENDED OVERALL SURVIVAL

IMBRUVICA® significantly extended overall survival vs chlorambucil

Statistically significant reduction in risk of death[1]

56%

HR=0.44
(95% CI: 0.21, 0.92)

41% of patients crossed over to IMBRUVICA®

Estimated survival rates at 24 months

95% IMBRUVICA®
(95% CI: 89, 97)

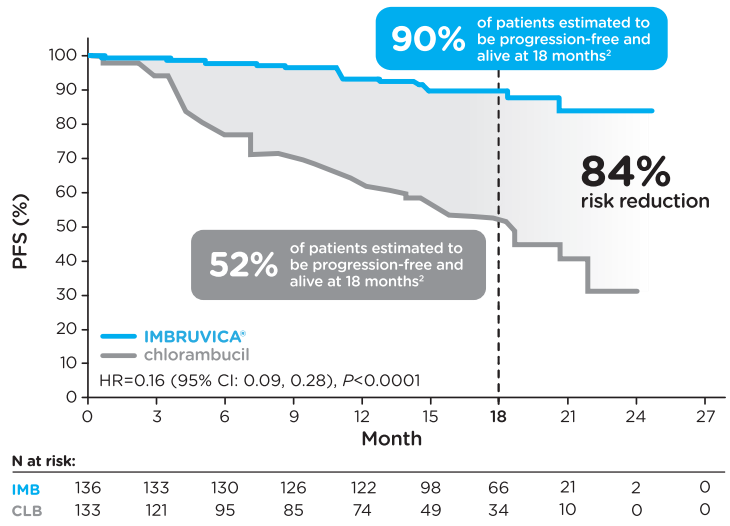
84% chlorambucil
(95% CI: 77, 90)

SECONDARY ENDPOINT: OVERALL SURVIVAL (OS)

- Median follow-up was 28 months[1]

PROLONGED PROGRESSION-FREE SURVIVAL

IMBRUVICA® significantly extended PFS vs chlorambucil



N at risk:

IMB	136	133	130	126	122	98	66	21	2	0
CLB	133	121	95	85	74	49	34	10	0	0

PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL (PFS)

- Median follow-up was 18 months[2]
- IMBRUVICA® median PFS not reached[1]
- Chlorambucil median PFS was 18.9 months (95% CI: 14.1, 22.0)[1]
- PFS was assessed by an Independent Review Committee (IRC) per revised International Workshop on CLL (IWCLL) criteria[1]

Adverse reactions ≥20% across CLL/SLL registration studies[1]

- Neutropenia
- Thrombocytopenia
- Anemia
- Diarrhea
- Musculoskeletal pain
- Nausea
- Rash
- Bruising
- Fatigue
- Pyrexia
- Hemorrhage

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

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, and WM) were neutropenia* (64%), thrombocytopenia* (63%), diarrhea (43%), anemia* (41%), musculoskeletal pain (30%), rash (29%), nausea (29%), bruising (29%), fatigue (27%), hemorrhage (21%), and pyrexia (21%).

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

The most common Grade 3 or 4 non-hematologic 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/SLL), 14% (MCL), and 11% (WM) of patients had a dose reduction due to adverse reactions.

Approximately 4%-10% (CLL/SLL), 9% (MCL), and 6% (WM) of patients discontinued due to adverse reactions. Most frequent adverse reactions leading to discontinuation were pneumonia, hemorrhage, atrial fibrillation, rash, and neutropenia (1% each) in CLL/SLL patients and subdural hematoma (1.8%) in MCL patients.

DRUG INTERACTIONS

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

CYP3A Inducers - Avoid coadministration 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 see the Brief Summary on the following pages.

References: 1. IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC 2016. **2.** Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.

To learn more, visit
IMBRUVICAHCP.com

imbruvica®
(ibrutinib) 140mg capsules

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/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) *[see Clinical Studies (14.2) in Full Prescribing Information].*

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL) 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 (intracranial hemorrhage [including 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 and patients should be monitored for signs of bleeding.

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

Infections: Fatal and non-fatal infections have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 29% of patients *[see Adverse Reactions].* Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA. Evaluate patients for fever and infections and treat appropriately.

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%) based on laboratory measurements occurred in patients treated with single agent 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, hypertension, 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. Atrial fibrillation should be managed appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines *[see Dosage and Administration (2.3) in Full Prescribing Information].*

Hypertension: Hypertension (range, 6 to 17%) has occurred in patients treated with IMBRUVICA with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Second Primary Malignancies: Other malignancies (range, 5 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 13%).

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

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

ADVERSE REACTIONS

The following 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]*
- Hypertension *[see Warnings and Precautions]*
- Second Primary Malignancies *[see Warnings and Precautions]*
- Tumor Lysis Syndrome *[see Warnings and Precautions]*

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

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

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

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

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

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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	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/Small Lymphocytic Lymphoma: The data described below reflect exposure in one single-arm, open-label clinical trial and three randomized controlled clinical trials in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1 included 51 patients with previously treated CLL, Study 2 included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, Study 3 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil and Study 4 included 578 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab.

The most commonly occurring adverse reactions in Studies 1, 2, 3 and 4 in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1, 2, 3 and 4 discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1: Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies*	12*	0
Vascular disorders	Hypertension	16	8

* One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL/SLL (N=51) in Study 1

	Percent of Patients (N=51)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	69	12
Neutrophils Decreased	53	26
Hemoglobin Decreased	43	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

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 in patients with previously treated CLL/SLL.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 2

Body System Adverse Reaction	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				
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.

Study 3: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in Study 3.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 3

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
Eye Disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0

IMBRUVICA® (ibrutinib) capsules

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 3 (continued)

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular Disorders				
Hypertension*	14	4	1	0
Nervous System Disorders				
Headache	12	1	10	2

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

Study 4: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in Study 4 in patients with previously treated CLL/SLL.

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients in Study 4

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	55
Thrombocytopenia*	34	16	26	16
Skin and subcutaneous tissue disorders				
Rash*	32	4	25	1
Bruising*	20	<1	8	<1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal Pain	12	1	8	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular Disorders				
Hemorrhage*	19	2	9	1
Hypertension*	11	5	5	2
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
Hyperuricemia	10	2	6	0

The system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
<1 used for frequency above 0 and below 0.5%

Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo + BR.

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 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in the WM trial.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (N=63)

Body System	Adverse Reaction	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
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 preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 10: 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.

Additional Important Adverse Reactions: *Diarrhea:* Diarrhea of any grade occurred at a rate of 43% (range, 36% to 63%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 15%) and Grade 3 in 3% (range, 0 to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 12 days (range, 0 to 627), of Grade 2 was 37 days (range, 1 to 667) and of Grade 3 was 71 days (range, 3 to 627). Of the patients who reported diarrhea, 83% had complete resolution, 1% had partial improvement and 16% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 88 days (range, 1 to 414 days). Of the patients with visual disturbance, 64% had complete resolution and 36% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 281 days).

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

Hepatobiliary disorders: hepatic failure (includes multiple terms)

Metabolic and nutrition disorders: tumor lysis syndrome *[see Warnings & Precautions]*

Skin and subcutaneous tissue disorders: anaphylactic shock, angioedema, urticaria

DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A (CYP3A).

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: *Risk Summary:* IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including malformations *[see Data].* If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

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

IMBRUVICA® (ibrutinib) capsules

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

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

Lactation: *Risk Summary:* There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

Females and Males of Reproductive Potential: *Pregnancy Testing:* Verify the pregnancy status of females of reproductive potential prior to initiating IMBRUVICA therapy.

Contraception:

Females: Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males: Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

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

Geriatric Use: Of the 839 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 21% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA *[see Clinical Studies (14.2) 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 cancer patients with mild to severe hepatic impairment by Child-Pugh criteria.

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 class B and C) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information].*

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

PATIENT COUNSELING INFORMATION

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

- *Hemorrhage:* Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions].*
- *Infections:* Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Warnings and Precautions].*
- *Atrial fibrillation:* Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions].*
- *Hypertension:* Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy *[see Warnings and Precautions].*
- *Second primary malignancies:* Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions].*
- *Tumor lysis syndrome:* Inform patients of the potential risk of tumor lysis syndrome and report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions].*
- *Embryo-fetal toxicity:* Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA *[see Warnings and Precautions].*
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the 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 (2.6) in Full Prescribing Information].*
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions].* Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions].*
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration.

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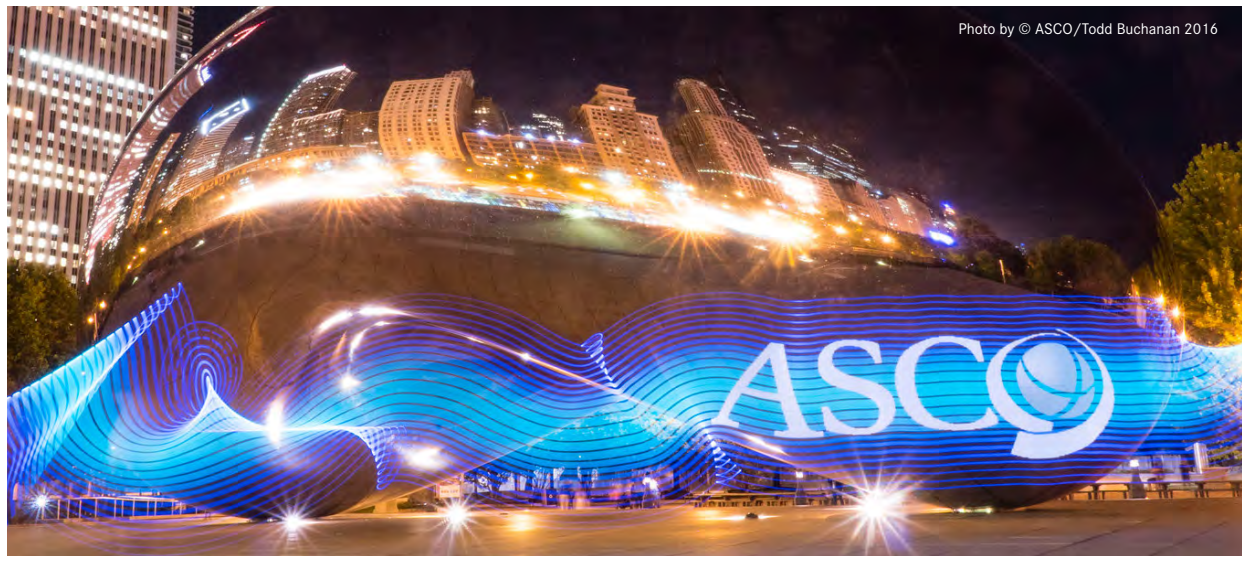

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Julie M. Vose, MD, MBA, FASCO, 2015-2016 president of the American Association of Clinical Oncology; introduces Vice President Joe Biden at the annual meeting.

Highlights From the Annual Meeting of ASCO

The fervor at this year's annual meeting of the American Society of Clinical Oncology (ASCO) received an added boost following the announcement, just a few days before the meeting, that Vice President Joe Biden would be addressing meeting participants. On the agenda, of course, was the proposal that gathered momentum following the declaration of the White House Precision Medicine Initiative: Cancer Moonshot.

The focus of the vice president's address was collaboration, data sharing, and mining big data. Prior to his speech at ASCO, Vice President Biden visited the Genomic Data Commons at the University of Chicago—a public database for clinical genomic data that is funded by the National Cancer Institute. Emphasizing the need for revamping the mindset of clinicians and researchers, he said, "No one knows the problem or the potential solutions better than all of you assembled here today. We not only need your continued scholarship and your incredible capacity, but we need some ideas on how to speed this process."

The meeting itself was a perfect melting pot of basic, clinical, health economic, and outcomes research in oncology. Progress in the field of immunotherapy was reported for both solid and liquid cancers, with clinical trial data on nivolumab and ipilimumab presented for small cell lung cancer, and nivolumab and OX40 agonists in several advanced solid tumors. However, lack of predictive biomarkers remains an ongoing challenge with these agents.

MIKE HENNESSY, SR

Although chimeric antigen receptor T cells, or CAR-T cells, continue to provide encouraging results for blood cancers, several questions remain unanswered, including the optimal cell dose, the ideal construct that can be used, and combining CAR-T cells with other immunotherapies. A bigger challenge, though, is the cost of these treatments, which currently ranges from $300,000 to $500,000 per patient.

The overall cost of cancer care, and the resulting burden on patients and their families, was also covered during several sessions. Researchers presented cost analysis that compared the cost of various treatment options and their benefit. Physicians are increasingly paying attention to the economic aspect of care, and several organizations have developed tools that providers can go to for assessing the "value" of available treatments.

We hope that this special issue provides a comprehensive overview of the annual meeting, and we thank you for your readership. You can receive updates on conferences and events held by *The American Journal of Managed Care* 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.

Web App Boosts Survival for Lung Cancer Patients

ANITA T. SHAFFER

Patients with lung cancer who participated in a Web-based system for reporting and tracking their symptoms achieved dramatic gains in survival compared with individuals who were followed with typical protocols, according to study results presented at the 2016 annual meeting of the American Society of Clinical Oncology (ASCO).

The MoovCare system made a difference for patients because it resulted in early detection of dangerous conditions or recurrences, resulting in healthier individuals who were better able to undergo optimal therapy and earlier supportive care that improved their quality of life, said lead study author Fabrice Denis, MD, PhD, during an ASCO press cast. The median overall survival (OS) rate for patients who used the MoovCare system was 19 months compared with 12 months for participants in the control group (HR, 0.325; *P* = .0025), after 20 months of follow-up. Additionally, 75% of the patients followed through MoovCare were still alive at 1 year versus 49% with standard procedures.

There also was a 50% reduction in the average number of imaging tests per patient per year with the use of the app, said Denis, a researcher at the Institut Interrégional de Cancérologie Jean Bernard in Le Mans, France. These improvements were achieved even though the relapse rates were similar for both groups: 49% among those who used the app and 51% among those with typical follow-up, researchers reported. However, performance scores stayed higher among patients who used MoovCare. As a result, 74% of these patients were able to undergo optimal therapy upon relapse compared with 33% who had not used the app (P<.001).

Denis said the need for an app in lung cancer is particularly pressing. "There are no standard follow-ups to detect relapse in patients," he said. "Relapses are frequent and often symptomatic. Symptomatic patients often wait, leading to health degradation and nonoptimal therapy."

MoovCare consists of a software application that patients or their caregiver use to report their symptoms. The algorithm analyzes the information for signals of potential relapse or complications and, if necessary, notifies the oncology care provider via e-mail. The app can be accessed on mobile and desktop devices.

Denis and colleagues tested the system in a phase 3 trial conducted at 5 medical centers in France. Results were reported for 121 patients in the intent-to-treat analysis who were randomized to use either the MoovCare system (n = 60) or routine follow-up (n = 61). The trial was stopped early at the interim analysis because of the positive results.

The study population consisted of patients with nonprogressive non–small cell lung cancer or small cell lung cancer at stages IIA through IV. Participants were required to have a performance score of 0 to 2 and a symptomatic score less than 7. All patients underwent chemotherapy before starting the trial and were permitted to continue tyrosine kinase inhibitor therapy, or maintenance therapy, throughout the study.

Patients in the MoovCare arm were required to self-report weekly for 12 clinical symptoms including asthenia, cough, dyspnea, and anorexia. Those with stage II through IIIA cancers also received computed tomography (CT) scans at 6-, 12-, and 24-month intervals while those with stage IIIB through IV cancers were scheduled for scans at 12 months and 24 months.

In the control arm, patients with stage II through IIIA cancers received scans every 6 months, while participants with stage IIIB through IV disease were scheduled for monthly scans starting at 3 months. Additional CT scans could be performed at the investigator's discretion for patients in both arms, Denis said.

The primary endpoint for the trial was OS, with the boundary for superiority set at *P* <.006. Secondary outcomes including performance score evaluation after first relapse, progression-free survival, and quality-of-life score using the standard FACT-L, FACT-G, and TOI questionnaires.

In response to questions about MoovCare's practicality, Denis said the system is easy to install on a computer and would simply require a doctor or nurse to monitor the e-mails. However, Patricia Ganz, MD, an ASCO commentator who served as moderator for the press cast, said drawing benefit from such a system would necessitate changes in US practices. She said that similar experiments in the United States found that information patients submit electronically does not generate action because of the cost of deploying personnel to monitor the data.

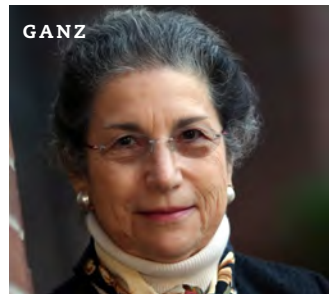
"We're trying to restructure how we deliver care so that we can be responsive to these kinds of changes and these tools where patients can report their symptoms and how they're doing on a regular basis," said Ganz, a professor at the UCLA Fielding School of Public Health/Department of Health Policy and Management. "If there's staff in the office who can respond, [it would] really make a difference in preventing emergency department visits, hospitalizations, and so forth."

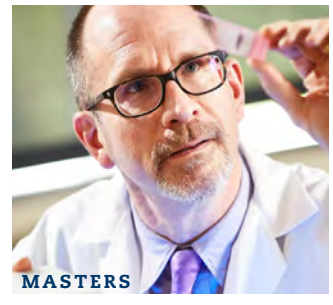
ASCO spokesman Gregory A. Masters, MD, a lung cancer specialist at the Helen F. Graham Cancer Center in Delaware, said the MoovCare system presents "one way to engage patients and allow them to take a more active role in their care."

He said this is particularly important in lung cancer. "Lung cancer is a unique cancer in some ways because many of these patients have a lot of guilt about their diagnosis. I think we see that more in lung cancer patients than in many other patients. Some patients don't want to bother the doctor or the nurse or the healthcare team with their symptoms, or they think [their symptoms] are not important."

Sivan Innovation, an e-health company headquartered in Jerusalem that developed MoovCare, said the system is the first Web application based on telemonitoring. The company said it would seek regulatory approvals for marketing it as a medical device and that a CE mark procedure is underway in Europe.

The company also said it would start rolling out the application in France in 2017, followed by elsewhere in Europe, the United States, Israel, and other countries. MoovCare also is in development for approximately 15 other cancer indications, notably lymphoma, in a partnership with Takeda France, the company said. **EBO**





REFERENCE

Denis F, Lethrosne C, Pourel N, et al. Overall survival in patients with lung cancer using a web-application-guided follow-up compared to standard modalities: results of phase III randomized trial. *J Clin Oncol.* 2016;34(suppl; abstract LBA9006).

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Cabozantinib Improves Survival in Renal Cell Carcinoma

JASON M. BRODERICK

Cabozantinib (Cabometyx) reduced the risk of death by 34% compared with everolimus (Afinitor) in patients with previously treated advanced renal cell carcinoma (RCC), according to updated data from the phase 3 METEOR trial presented at the 2016 annual meeting of the American Society of Clinical Oncology (ASCO).[1]

The results, which were simultaneously published in *The Lancet Oncology*,[2] showed a 4.9-month median overall survival (OS) benefit with cabozantinib. The risk of disease progression was reduced by 49% with the multi kinase inhibitor versus everolimus. Based on the METEOR trial's results, the FDA approved cabozantinib in April 2016 for patients with advanced RCC who had prior antiangiogenic therapy.[3]

"In the phase 3 METEOR trial, treatment with cabozantinib was associated with a significant improvement in overall survival, as well as progression-free survival and objective response rate compared with everolimus in patients with advanced renal cell carcinoma. Cabozantinib is a new standard for patients with advanced RCC after prior antiangiogenic therapy," lead author Toni Choueiri, MD, clinical director, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, said when presenting the data at ASCO.

In the METEOR study, 658 patients with clear cell RCC were randomized in a 1:1 ratio to receive daily cabozantinib at 60 mg (n = 330) or everolimus at 10 mg (n = 328). The median age of patients was approximately 62 years (range, 31 to 86 years). By Memorial Sloan Kettering (MSK) criteria, approximately 46% of patients in each arm were in the favorable prognostic risk category, 41% were intermediate, and 13% were poor.

A majority of patients in each arm had received 1 prior vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) (71%), with approximately 30% having received 2 or more prior VEGFR TKIs. Use of prior VEGFR TKIs included sunitinib (64% in the cabozantinib arm vs 62% in the everolimus arm), pazopanib (44% vs 41%), axitinib (16% vs 17%), and sorafenib (6% vs 9%). The rates of prior cytokines, programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors, and bevacizumab, between the cabozantinib and everolimus arms, were similar: 12% versus 16%, 5% versus 4%, and 2% versus 3%, respectively. Across the study, approximately 33% of patients had received radiotherapy and 86% of patients had undergone nephrectomy.

Median OS was 21.4 months (95% CI, 18.7-not estimable) for patients receiving cabozantinib versus 16.5 months (95% CI, 14.7-18.8) for those receiving everolimus (HR, 0.66; 95% CI, 0.53-0.83; $P = .0003$). The OS benefit with cabozantinib was sustained across all prespecified patient subgroups, including MSK risk groups, prior VEGFR TKIs, bone metastases, visceral bone metastases, and tumor MET status.

Commenting on the MET subgroup, Choueiri said, "The hazard ratio for overall survival in the MET-high versus MET-low expression group does suggest that patients do experience clinical benefit with cabozantinib regardless of MET expression level. This could reflect the broader target profile of cabozantinib." He also noted that there was a similar OS benefit among patients whose only prior VEGFR TKI was either sunitinib or pazopanib. The HR for OS was 0.66 for both subgroups.

Among patients with bone metastases, the median OS with cabozantinib was 20.1 months versus 12.1 months with everolimus (HR, 0.54; 95% CI, 0.34-0.84).

The updated median progression-free survival (PFS), by independent, review was consistent with the initial PFS analysis: 7.4 months with cabozantinib compared with 3.9 months with everolimus (HR, 0.51; 95% CI, 0.41-0.62; $P <.0001$). The PFS with cabozantinib was superior to everolimus across all subgroups.

The median duration of treatment with cabozantinib was 8.3 versus 4.4 months with everolimus. The objective response rate (ORR), per independent review, was 17% (95% CI, 13-22) in the cabozantinib arm versus 3% (95% CI, 2-6) in the everolimus arm. The stable disease rates were 65% versus 62% and the progressive rates were 12% versus 27%, respectively. The investigator-assessed ORR was 24% (95% CI, 19-29) with cabozantinib compared with 4% (95% CI, 2-7) with everolimus. Stables disease rates, per investigator assessment, were 63% in both arms and the progressive disease rates were 9% and 27%, respectively.

The updated safety results were consistent with those initially reported. The most common all-grade adverse events (AEs) with cabozantinib were diarrhea (75%), fatigue (59%), nausea (52%), decreased appetite (47%), palmar-plantar erythrodysesthesia syndrome (43%), hypertension (37%), weight decrease (34%), and vomiting (34%). With everolimus, the most common all-grade AEs were fatigue (48%), anemia (39%), decreased appetite (35%), cough (34%), and dyspnea (30%).

The most common grade 3/4 AEs with cabozantinib were hypertension (15%), diarrhea (13%), and fatigue (11%) compared with anemia (17%), fatigue (7%), and hyperglycemia (5%) with everolimus. Serious AEs occurred in 39% of the cabozantinib group and 40% of the everolimus arm. Dose reductions were required for 62% and 25% of patients in the cabozantinib and everolimus arms, respectively.

Treatment discontinuation due to AEs was observed in 12% of patients in the cabozantinib arm and 11% in the everolimus arm. There was 1 treatment-related death in the cabozantinib cohort and 2 deaths among the patients who received everolimus. Following treatment discontinuation, some of the subsequent anticancer therapies received included VEGFR TKIs (24% in the cabozantinib arm vs 47% in the everolimus arm), everolimus (29% vs 5%), and PD-1/PD-L1 agents (5% vs 6%).

"We [were] excited to share the detailed overall survival results from the METEOR trial with the oncology community at this year's ASCO annual meeting," Michael M. Morrissey, PhD, president and chief executive officer of Exelixis, which is co-developing cabozantinib with Ipsen, said in a statement. "The 5-year survival rate for patients diagnosed with advanced kidney cancer is only 12%, underscoring the need for new treatment options that help patients live longer while delaying the progression of their disease. Critically, Cabometyx—the first FDA-approved therapy to demonstrate a benefit in all three key efficacy parameters—now shows consistent survival benefit across all subgroups of patients evaluated in METEOR."[4]

Exelixis announced in May 2016 that cabozantinib also demonstrated efficacy in the frontline setting for RCC. In the phase 2 CABOSUN trial, cabozantinib significantly improved PFS, compared with sunitinib, in treatment-naïve patients with advanced RCC. Exelixis plans to submit the full CABOSUN results for presentation at an upcoming medical meeting and communicate with regulatory authorities about a potential first-line cabozantinib indication in RCC. **EBO**

> **"The hazard ratio for overall survival in the MET-high versus MET-low expression group does suggest that patients do experience clinical benefit with cabozantinib regardless of MET expression level. This could reflect the broader target profile of cabozantinib."**
>
> —TONI CHOUEIRI, MD

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REFERENCES

1. Choueiri TK, Powles T, Escudier BJ, et al. Overall survival (OS) in METEOR, a randomized phase 3 trial of cabozantinib (Cabo) versus everolimus (Eve) in patients (pts) with advanced renal cell carcinoma (RCC). *J Clin Oncol*. 2016;34(suppl; abstract 4506).
2. Choueiri TK, Escudier BJ, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial [published online June 5, 2016]. *Lancet Oncol*. 2016. doi:10.1016/S1470-2045(16)30107-3.
3. Dangi-Garimella S. FDA approves cabozantinib for advanced renal cell carcinoma. *The American Journal of Managed Care* website. http://www.ajmc.com/newsroom/fda-approves-cabozantinib-for-advanced-renal-cell-carcinoma. Published April 25, 2016. Accessed June 28, 2016.
4. Exelixis and its partner Ipsen announce phase 3 trial results of CABOMETYX (cabozantinib) tablets demonstrating significant overall survival benefit for previously treated patients with advanced renal cell carcinoma presented at ASCO [press release]. Paris, France, and South San Francisco, CA: Ipsen; June 5, 2016. http://www.businesswire.com/news/home/20160605005052/en/Exelixis-partner-Ipsen-announce-phase-3-trial.

ASCO'S TAPUR Study Continues to Grow

CATE DOUGLASS

The American Society of Clinical Oncology (ASCO)'s first-ever clinical trial is growing with the addition of its seventh and eighth pharmaceutical companies, Bayer and Merck, and 30 additional trial participants. ASCO kicked off its study, Targeted Agent and Profiling Utilization Registry (TAPUR), on March 14, 2016, in an effort to evaluate molecular-targeted cancer drugs, as well as to discover additional uses of these drugs outside of their previously FDA-approved purposes.[1] Since the study's inception, 18 participants have enrolled, with another 31 individuals who are either giving consent to participate or who are completing the screening process.

The number of study participants isn't the only statistic growing. TAPUR is currently underway in 37 clinical sites across the United States with additional locations in the works. About 100 clinical sites have already expressed interest in taking part in the study. And with the addition of Bayer and Merck to the 6 pharmaceutical companies that previously agreed, the study researchers are able to test a host of medications and combination therapies.

Bayer and Merck join Astellas, AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Genentech, and Pfizer to provide 17 drugs in 15 different targeted therapy options for participants with advanced solid tumors, multiple myeloma, or B cell non-Hodgkin lymphoma. "TAPUR addresses a critical priority for achieving the promise of precision medicine: identifying existing, effective treatments for cancers based on their genomic profiles," Richard L. Schilsky, MD, FASCO, chief executive officer of ASCO, said in a statement. "Since only about 5% of adult patients participate in oncology clinical trials, creative approaches like TAPUR, whose study design is grounded in real-world clinical practice, are needed to gather information that will benefit future patients."

The TAPUR study is, in part, run by employing the Syapse Precision Medicine Platform, which automates the eligibility assessment, drug ordering, study workflow (patient registration), and data collection sections of the study process. The Syapse-TAPUR application additionally provides the study with drug options based on genomic data and is directly responsible for acquiring these study drugs, which are dispensed from Cardinal Health Specialty Pharmacy.

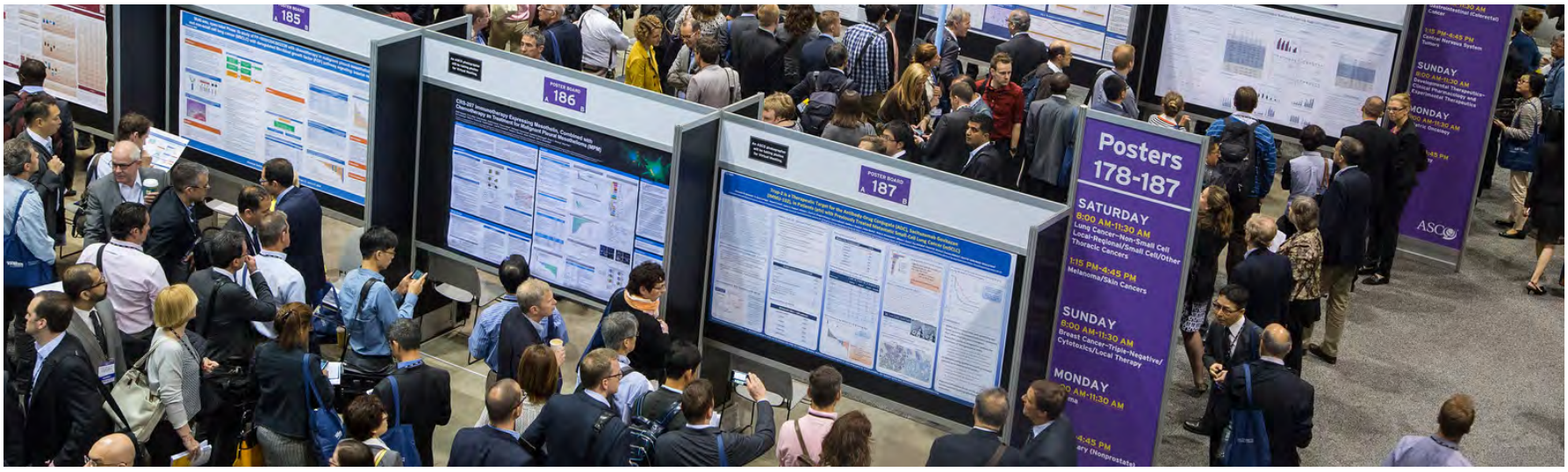
Additionally, ASCO and the Research Advocacy Network have teamed up to launch a sub-study that seeks to help the oncology community understand how tumor genomic testing is currently being used in the clinical world by oncologists, as well as assist in educating providers and patients on genomic testing in general. This sub-study runs concurrently with TAPUR: 2 brief surveys are administered to physicians at specific time points before and after TAPUR application. **EBO**

"TAPUR addresses a critical priority for achieving the promise of precision medicine: identifying existing, effective treatments for cancers based on their genomic profiles."

—RICHARD L. SCHILSKY, MD, FASCO

REFERENCE

1. Dangi-Garimella S. TAPUR study promises options for patients with advanced cancer. *The American Journal of Managed Care* website. http://www.ajmc.com/newsroom/tapur-study-promises-options-for-patients-with-advanced-cancer. Published March 14, 2016. Accessed June 20, 2016.



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Nivolumab Safe in Glioblastoma

SURABHI DANGI-GARIMELLA, PHD

Glioblastoma is the most common primary brain tumor in adults, with a median survival of 15 to 18 months and a 5-year survival rate of less than 5%. Most patients experience recurrence post surgery, and treating the recurrent tumor has not had much impact on survival outcomes so far.

At the annual meeting of the American Society of Clinical Oncology, held June 3-7, 2016, in Chicago, phase 1 data from the CheckMate 143 trial was presented during a poster session. The trial was designed to evaluate the safety and tolerability of nivolumab, alone or in combination with ipilimumab, in patients with recurrent/progressive glioblastoma (phase 1); the phase 3 study is designed to evaluate the efficacy of nivolumab monotherapy compared with bevacizumab in the same population of patients.

Eligible patients had a first recurrence of glioblastoma after radiation and temozolomide. Exclusion criteria included more than 1 recurrence of glioblastoma and prior treatment with bevacizumab or other antiangiogenic treatment.

In cohort 1, 20 patients were randomized 1:1 to receive nivolumab 3 mg/kg (N3) every 2 weeks or nivolumab 1 mg/kg (N1) with ipilimumab 3 mg/kg (I3) every 3 weeks for 4 doses, followed by N3 every 2 weeks. Patients in cohort 1b (n = 20) received N3 with ipilimumab 1 mg/kg (I1) every 3 weeks for 4 doses followed by N3 every 2 weeks. Treatment continued until disease progression or unacceptable toxicity.

The study found no grade 5 treatment-related adverse events (TRAEs). Nivolumab alone did not cause any grade 3 to 4 TRAEs. Discontinuation due to adverse events (AEs) was seen in 1 patient in the N3 arm, 5 patients in the N1 + I3 arm, and 2 patients in the N3 + I1 arm. These AEs included diabetic ketoacidosis, hypocalcemia, hypomagnesemia, hy-

Nivolumab and ipilimumab can be safely administered to patients with recurrent glioblastoma; their adverse-event profile is consistent with that observed in other tumor types.

perthyroidism, colitis, diarrhea, cholecystitis, sepsis, muscular weakness, malignant neoplasm progression, being in a confused state, acute kidney injury, hypotension, and increased alanine aminotransferase, aspartate aminotransferase, amylase, and lipase.

TRAEs with potential immunologic etiology were observed in the following study arms:

- Nivolumab monotherapy arm (5 patients)
- N1 + I3 (10 patients; 6 were grade 3-4)
- N3 + I1 (14 patients; 3 were grade 3-4)

In cohort 1, the study observed:

- An objective response rate in 1 patient (N3)
- A partial response in 1 patient (N3)
- Stable disease in 5 (N3) and 4 (N1 + I3) patients
- Progressive disease in 3 (N3) and 6 (N1 + I3) patients

In cohort 2, the study identified 10 patients with stable disease and 9 with progressive disease.

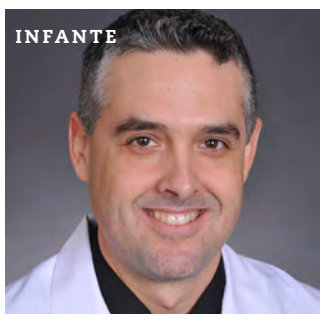
Based on their findings, the authors concluded that both nivolumab and ipilimumab can be safely administered to patients with recurrent glioblastoma and that the AE profile was consistent with that observed in other tumor types. **EBO**

REFERENCE

Reardon DA, Sampson JH, Sahebjam S, et al. Safety and activity of nivolumab (nivo) monotherapy and nivo in combination with ipilimumab (ipi) in recurrent glioblastoma (GBM): updated results from checkmate-143. *J Clin Oncol.* 2016;34(suppl; abstract 2014).

Promising Results With Combination Immunotherapy in Solid Tumors and Leukemia

SURABHI DANGI-GARIMELLA, PHD



As immunotherapy—particularly the checkpoint inhibitors—continues to show promise in solid as well as liquid tumors, clinicians have been evaluating these agents in combination to improve efficacy and outcomes. During a June 4, 2016 session during the annual meeting of the American Society of Clinical Oncology, in Chicago, the results from some of these trials were shared. Some of the questions that were addressed during the session included:

- How do we use the growing number of next-generation checkpoint inhibitors?
- How do we use them in combination with vaccines, radiation, chemotherapy, and other modalities?
- Do we need to investigate biomarkers other than the expression of programmed death ligand-1 (PD-L1)?

COMBINING NIVOLUMAB AND IPILIMUMAB IN SCLC

Scott Joseph Antonia, MD, PhD, chair, Department of Thoracic Oncology Department and program leader of the Immunology Program, H. Lee Moffitt Cancer Center, discussed results of the CheckMate 032 trial, in which the programmed death-1 (PD-1) receptor inhibitor nivolumab was used alone or combined with ipilimumab in the treatment of recurrent small cell lung cancer (SCLC).[1]

It has been over a year since nivolumab was approved in the United States for patients who have progressed on their existing treatment for metastatic non-small cell lung cancer (NSCLC)—however, nivolumab was rejected in the United Kingdom by the National Institute for Health and Care Excellence, or NICE, for patients with advanced NSCLC.[2] Antonia said that there's been trivial progress with SCLC, which he described as being a very stubborn disease. While majority of patients respond to frontline chemotherapy, a majority of them relapse, and then the response rates for the next line of treatment plummets, he explained.

Antonia said that CheckMate 032 was designed to evaluate nivolumab, with or without ipilimumab, in advanced tumors including SCLC. Eligibility criteria for trial participation was advanced SCLC with progressive disease after 1 or more platinum-based chemotherapy, regardless of platinum sensitivity or tumor PD-L1 expression. The primary end point of the trial was objective response rate (ORR), with secondary end points of safety, overall survival (OS), progression-free survival (PFS), and biomarker expression. The 216 patients enrolled in the trial were divided into 3 cohorts:

- 98 patients were treated with nivolumab alone, at a dose of 3 mg/kg (N3)
- 61 patients were treated with nivolumab 1 mg/kg and ipilimumab 3 mg/kg (N1/I3)
- 54 patients were treated with nivolumab 3 mg/kg and ipilimumab 1 mg/kg (N3/I1)

Based on the data presented, a majority of the patients in each cohort expressed less than 1% PD-L1. Additionally, 59% of patients in the nivolumab-alone cohort, 48% in the N1/I3 cohort, and 58% in the N3/I1 cohort had received 2 or more prior lines of treatment.

Antonia showed toxicity data for the trial, saying that toxicity was greater in the combination arms. "Three treatment-related deaths were observed among the 114 patients treated with the combination therapy. However, patients were willing to remain on their treatment despite the toxicity," he said. Response rates doubled with the combination therapy, including in platinum-resistant patients. Majority of the responders had a rapid, durable response, and response was independent of PD-L1 expression. Antonia said that PD-L1 negative patients responded just as well. Median OS, he showed, was 7.7 months for the N1/I3 cohort and 6 months for the N3/I1 cohort—significantly greater than the 4 months

(continued on **SP355**)

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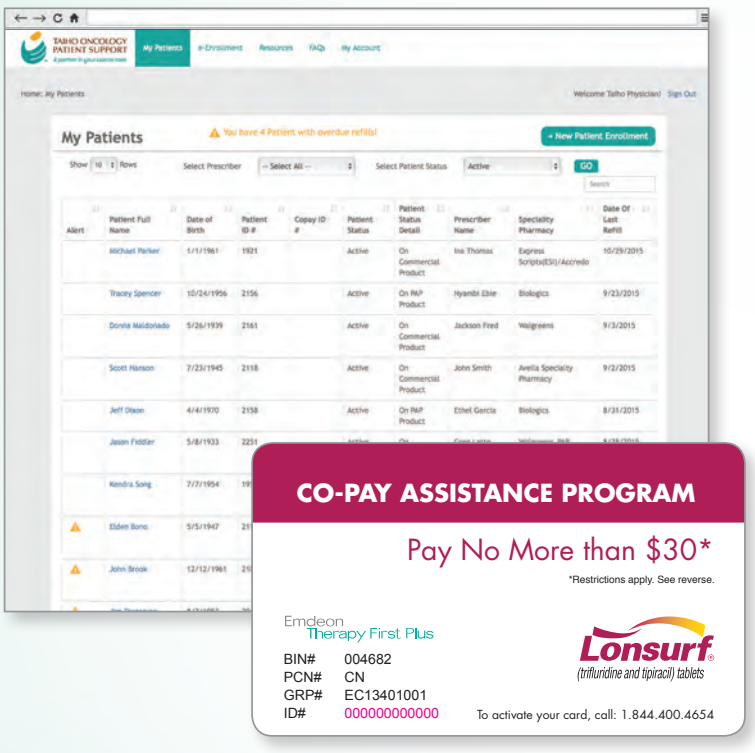

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Please see Important Safety Information and brief summary of Prescribing Information on the following pages.

Lonsurf® (trifluridine and tipiracil) tablets

TAIHO ONCOLOGY

Lonsurf®
(trifluridine and tipiracil) tablets

Indication

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

Important Safety Information

WARNINGS AND PRECAUTIONS

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

Learn more at LONSURFhcp.com

TAIHO ONCOLOGY

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

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

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

4 CONTRAINDICATIONS
None.

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

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

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

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

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

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

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

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

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

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

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

Table 2 Laboratory Test Abnormalities

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

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

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

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

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

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

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

Data

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

8.3 Females and Males of Reproductive Potential

Contraception

Females

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

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

Males

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

8.4 Pediatric Use

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

Animal Data

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

8.5 Geriatric Use

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

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

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

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

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

8.8 Ethnicity

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

10 OVERDOSAGE

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

There is no known antidote for LONSURF overdosage.

17 PATIENT COUNSELING INFORMATION

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

Severe Myelosuppression:

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

Gastrointestinal toxicity:

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

Administration Instructions:

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

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

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

Embryo-Fetal Toxicity:

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

Lactation:

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

TAIHO ONCOLOGY, INC.

(continued from **SP350**)

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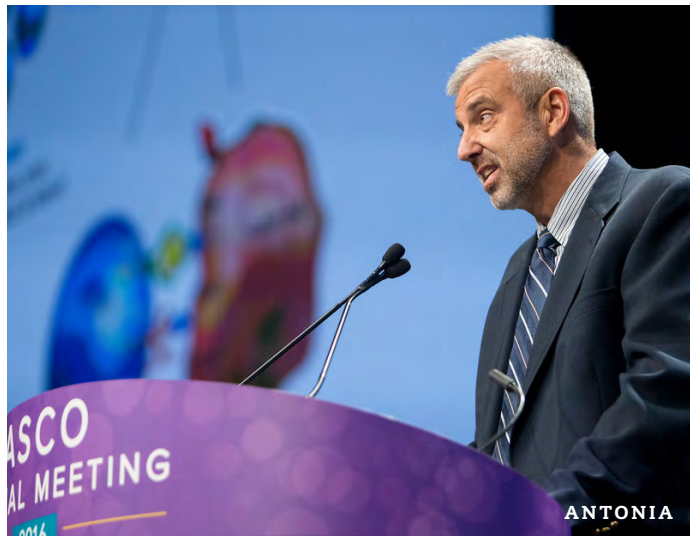

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observed in patients treated with nivolumab alone. Further, the 1-year OS rate was:

- 33% in the single-drug arm
- 43% in the N1/I3 arm
- 35% in the N3/I1 arm

Antonia concluded that the survival rates from this early study are encouraging. The safety profile observed in the CheckMate 032 trial for SCLC was no different from that observed in other diseases treated with the combination, with higher rates of adverse events (AEs) compared with nivolumab alone. Dose expansion trials and studies in combination with other agents are ongoing, Antonia said, and include:

- CheckMate 032 expansion study in 250 patients
- CheckMate 331, nivolumab versus chemotherapy (topotecan or amrubicin) in patients with relapsed SCLC
- CheckMate 451 nivolumab versus N1/I3 versus placebo in patients with extensive SCLC following platinum-based first-line

Based on the results of this study, nivolumab 1 mg/kg and ipilimumab 3 mg/kg was the dose of choice for a phase 3 study with this combination in SCLC patients.

COMBINING PD-L1 INHIBITORS WITH OX40 AGONISTS

Jeffrey R. Infante, MD, director of the drug development program at Sarah Cannon Research Institute, presented a phase lb dose escalation study of an OX40 receptor agonist, in combination with a PD-L1 inhibitor, in patients with advanced solid tumors.

OX40 agonists, Infante said, have a dual mechanism of action: they inhibit regulatory T cells and costimulate effector T cells. This can definitely be complemented by the PD-L1 inhibition. Being a phase 1 study, the primary objective of their trial was to evaluate the safety and tolerability of combining the PD-L1 inhibitor atezolizumab with the OX40 inhibitor MOXR0916. MOXR0916 is a humanized effector-competent agonist IgG1 monoclonal antibody. The secondary objectives of the study included:

- Establishing a phase 2 dose
- Determining pharmacokinetics and immunogenicity of agents
- Preliminary efficacy
- Identifying biomarkers

A total of 51 patients were enrolled in the study, with a median age of 58 years. The most common tumor types were NSCLC, renal cell carcinoma (RCC), ovarian cancer, gastroesophageal (GE) junction cancer, and soft-tissue sarcoma. A log that detailed whether patients had received prior treatment with an anti–PD-1 or anti–PD-L1 agent was maintained. A 3+3 dose-escalation was conducted with a 21-day window to evaluate dose-limiting toxicity (DLT), Infante explained. Escalating doses of MOXR0916, in combination with a fixed 1200-mg dose of atezolizumab, were administered every 3 weeks. An expansion cohort to enable immune profiling of serial tumor biopsies was also enrolled in the trial. Prior immunotherapy with adequate washout was allowed if there was no history of grade 3 or greater immune-mediated AEs.

Infante said that the combination was well tolerated overall, with no DLT, deaths, or grade 4 or higher toxicity. A grade 3 pneumonitis in 1 patient was controlled with antibiotics and steroids. "No truly dose-dependent AE was observed," he concluded.

The current expansion regimen is MOXR0918 at 300 mg in combination with atezolizumab 1200 mg, every 3 weeks. Significantly, the study did observe PD-L1 modulation in patients who had had immediate prior therapy with single-agent anti-OX40 or anti–PD-1.

Efficacy studies, Infante said, are ongoing for the combination in melanoma, RCC, NSCLC, urothelial carcinoma, and triple-negative breast cancer.

DISCUSSANT'S COMMENTS

Following the 2 presentations, Jedd D. Wolchok, MD, PhD, chief of the Melanoma and Immunotherapeutics Service at Memorial Sloan Kettering Cancer Center, discussed the findings. Expressing his excitement with the results that were presented, Wolchok said that questions remain. "We need additional numbers on patients along with further information on the nature of the response," he said, including whether the combination treatment generates a deeper response. Information on the PD-L1 status in each group is also important to understand, Wolchok said. "We also need studies that evaluate other agents for combination studies."

With respect to the OX40 study, Wolchok said that lab-based studies have shown a 100% survival response in mice treated with an OX40 agonist with azetolizumab. He was quite impressed by the biomarker analysis done by the study group, evaluating the upregulation of PD-L1. "OX-40 is a potentially promising agent," Wolchok concluded. **EBO**

> **"We need additional numbers on patients along with further information on the nature of the response. We also need studies that evaluate other agents for combination studies."**
>
> –JEDD D. WOLCHOK, MD, PHD

> **Response rates doubled with the combination therapy, including in platinum-resistant patients. Majority of the responders had a rapid, durable response, independent of PD-L1 expression.**

REFERENCES

1. Antonia SJ, López-Martin JA, Bendell JC, et al. Checkmate 032: Nivolumab (N) alone or in combination with ipilimumab (I) for the treatment of recurrent small cell lung cancer (SCLC). *J Clin Oncol*. 2016;34 (suppl; abstract 100).
2. Dangi-Garimella S. Nivolumab approved by EC for melanoma, rejected by NICE for lung cancer. *The American Journal of Managed Care* website. http://www.ajmc.com/newsroom/nivolumab-approved-by-ec-for-melanoma-rejected-by-nice-for-lung-cancer. Published May 12, 2016. Accessed June 4, 2016.

CAR-T Cells in Leukemia and Lymphoma

SURABHI DANGI-GARIMELLA, PHD

> **“Adoptive therapy with CD19 CAR-T cells of defined subset composition results in durable [complete response] in a high fraction of patients with relapsed/refractory ALL, NHL, and CLL.”**
>
> —CAMERON JOHN TURTLE, MBBS, PHD

Cancer immunotherapy research has seen tremendous progress since the first checkpoint inhibitor, ipilimumab was approved in 2011. While combination immunotherapies are now being developed, they have their limitations because not all patients respond to the checkpoint inhibitors. Additionally, the absence of predictive biomarkers places limitations with respect to choosing positive responders for trial enrollment.

Chimeric antigen receptor T cells (CAR-T cells) are T cells genetically engineered to express a chimeric receptor on their cell surface. These cells are derived from the patient and then modified in vitro, before being reintroduced in the patient.[1] This kind of immunotherapy has been gaining a lot of ground in clinical trials.

At the annual meeting of the American Society of Clinical Oncology, Cameron John Turtle, MBBS, PhD, Fred Hutchinson Cancer Research Center, presented results from a phase 1/2 trial in which patients with relapsed or refractory CD19+ B-cell malignancies received CD19 CAR-T cells. Rate of durable complete response in acute lymphocytic leukemia (ALL), non-Hodgkin lymphoma (NHL), and chronic lymphocytic leukemia (CLL), following immunotherapy with optimized lymphodepletion, was evaluated.

Thirty six patients with ALL were included in the trial, 33 of whom received products formulated in the defined composition; 26 were treated in an outpatient facility. Patients with ALL, Turtle said, had a high rate of minimal residual disease–negative complete response (CR), which was assessed using multiple techniques:

- Morphologic bone marrow
- Bone marrow by flow cytometry
- Deep sequencing
- Extramedullary disease

Turtle listed the 2 key observations for the patients with ALL:

- In a subset of patients treated with cyclophosphamide or cyclophosphamide/lymphodepletion, an anti-CAR immune response was observed.
- Addition of fludarabine to cyclophosphamide lymphodepletion improved CAR-T cell expansion and persistence.

Kaplan-Meier survival plots showed that over time, including fludarabine improved both disease-free and overall survival (OS) in patients with ALL.

Similarly, in patients diagnosed with NHL, the objective response rate (ORR) and CR was much improved following inclusion of fludarabine in the regimen. A high response rate in high-risk CLL patients was observed. In NHL, the ORR for patients treated with cyclophosphamide/lymphodepletion and fludarabine, was 84%. Additionally, CAR-T cell expansion and persistence, and OS and progression-free survival were better in patients whose regimen included fludarabine.

With respect to toxicity, Turtle said that overall the treatment is manageable. A majority of patients with ALL had very mild cytokine release syndrome (CRS); 90% with NHL had mild CRS, but did not require admission to the intensive care unit. Similarly, a majority of patients with CLL had mild CRS. The highest rate of neurotoxicity was observed in patients with ALL (39%), followed by CLL (23%), and least in NHL (20%).

Turtle concluded, “Adoptive therapy with CD19 CAR-T cells of defined subset composition results in durable CR in a high fraction of patients with relapsed/refractory ALL, NHL, and CLL.” Optimizing the dosing regimen, he said, improved clinical outcomes in patients with ALL and NHL.

EXPERT FEEDBACK

David L. Porter, MD, Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, provided comments on the study presented by Turtle.

Porter explained that targeted cellular immunotherapy has the potential to overcome many limitations of conventional chemotherapy and other immunotherapy. CAR-T cells can be a perfect blend of antibody therapy, cellular therapy, and vaccine therapy, he said.

Porter was quite impressed by the data presented by Turtle, especially in patients with relapsed and refractory ALL. He added that, “Relapse after CR in CLL is unusual, and we expect the current CR rate of 25% to 45% will be sustained.”

Several questions and issues remain unanswered with CAR-T cells, according to Porter.

- We are yet to identify the best CAR construct
- We don’t know the ideal cell composition
- Can they be switched on and off?
- Is there an ideal cell dose?
- What’s the ideal target?
- Can we combine CARs with other immune therapies?

Another limitation of this treatment, for both CLL and NHL, is the low CR rate of 25% to 50%. “How can this response rate be boosted?” asked Porter. To overcome some of these issues, Porter recommended developing a third-party donor of universal CAR-T cells.

In the future, Porter sees tremendous potential in tapping the synergism between CAR-T cells and checkpoint inhibitors. “Checkpoint activity may reduce CAR-T cell response, so it’s logical to combine the 2,” he concluded. **EBO**

REFERENCE

Dangi-Garimella S. A new method to fight cancer: The body’s own immune system. *The American Journal of Managed Care* website. http://www.ajmc.com/journals/evidence-based-oncology/2014/august-2014/a-new-method-to-fight-cancer-the-bodys-own-immune-system. Posted August 25, 2014. Accessed June 20, 2016.

Zeroing in on Predictive Biomarkers for Cancer Immunotherapy

SURABHI DANGI-GARIMELLA, PHD

Biomarkers to identify positive responders to checkpoint inhibitors have proven a challenging task for drug developers. While several clinical trials have tried to identify a programmed death-1 (PD-1) or programmed death ligand-1 (PD-L1) expression–dependent response, it's been an uphill task. During a clinical session at the annual meeting of the American Society of Clinical Oncology (ASCO), researchers were tasked with sharing their data on any breakthroughs or leads with biomarkers for these agents.

MISMATCH REPAIR DEFICIENCY IN CRC

During his talk, Programmed Death-1 Blockade in Mismatch Repair Deficient Colorectal Cancer, Luis A Diaz, Jr, MD, medical oncologist, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, provided an update on the progress of using mismatch repair (MMR) deficiency as a marker for predicting response to PD-1 receptors. A presentation at ASCO last year by his group generated a lot of interest, because it indicated that a patient's MMR status can be used to predict their response to the PD-1 inhibitor pembrolizumab, in colorectal cancer (CRC).[1]

Microsatellite instability resulting from genetic and epigenetic MMR is responsible for the development of CRC, Diaz said, adding that a majority of patients who participated in their trial were young and had Lynch syndrome or hereditary colon cancer.

MMR-deficient colon cancers are densely infiltrated with CD8+T cells and regress when treated with anti–PD-1 antibodies. This antitumor response is thought to be potentiated by somatic mutations, which when expressed as proteins, result in immunogenic neo-antigens that can be recognized by the patient's immune system.

The current study recruited patients diagnosed with CRC who were either deficient (n = 28) or proficient (n = 25) in MMR. Patients were treated with the anti–PD-1 antibody, pembrolizumab, at a dose of 10 mg/kg, every 2 weeks. The median age of MMR-deficient participants was significantly younger (49 years) compared with those who had MMR-proficient tumors (62 years).[2]

An immediate biochemical response to treatment was observed in those with MMR-deficient tumors, measured as the levels of carcinoembryonic antigen. At 30-months follow-up, median overall survival (OS) in the MMR-proficient cohort was 5.98 months, while the MMR-deficient cohort is yet to reach a median OS. Additionally, progression-free survival (PFS) in MMR-proficient patients was 2.3 months, but PFS was not reached in the MMR-deficient patients. The objective response rate was 0% and 57% in the MMR-proficient and MMR-deficient patients, respectively, while the disease control rate was 16% and 89%, respectively.

Diaz said that 50% of patients presented with complete and durable response. Five of the 28 MMR-deficient patients had reached the 2-year mark following initiation of treatment and were no longer being treated with pembrolizumab. "They are on active surveillance," Diaz said.

He had several thoughts on what this data would mean in the long term:

- Is it time to think of treating MMR-deficient tumors with anti–PD-1 agents in a histology-independent manner?
- How do we evaluate the management of patients who have a stable response following 2 years on a PD-1 inhibitor?
- Do we need to figure the molecular etiology of primary and secondary resistance in these tumors?

The discussant for the session, Alexandra Snyder Charen, MD, medical oncologist, Memorial Sloan Kettering Cancer Center, wondered about the assessment of mutation load in the clinical setting. "Would it be possible to use genetic panels such as next-generation sequencing (NGS) panels in the clinic?" While mutation load determined using NGS is a potential biomarker, the limited sample size makes it hard to assess the actual utility and value.

However, there is a trend indicating that there is a critical threshold for mutation burden for specific disease (including melanoma)—higher mutation burden can improve patient response. "Why does mutation burden matter?" Charen asked. Mutations create neo-antigens, which create abnormal proteins which are then presented to the immune system by antigen presenting cells (APCs).

Charen pointed out several questions that remain unanswered:

- Does mutation load matter in dual checkpoint blockade–treated patients?
- What factors lead to primary and acquired resistance in tumors expected to respond to checkpoint blockade?
  - Do they upregulate other checkpoints or are the APCs modified or missing pathways?

Charen is hopeful that peripheral testing, using blood-based biomarkers could help make progress in the field. However, a significant challenge remains integration of this multivariable data in a statistically and biologically meaningful manner in the clinic.


DIAZ


CHAREN


JOHNSON

NGS COULD BE THE ANSWER

Another approach to identifying a biomarker for checkpoint inhibitors is the use of NGS. Douglas Johnson, MD, MSCI, assistant professor of Medicine, Vanderbilt Ingram Cancer Center, presented results of his group's assessment of somatic mutations in archived samples from patients with melanoma who had been treated with PD-1 inhibitors. The objective was to determine a correlation, if any, between the number and type of somatic mutations and outcomes following PD-1 inhibition.

Johnson said that many elegant studies have been conducted to identify PD-1/PD-L 1 biomarkers to predict response. Some of these strategies include identifying the presence, location, and clonal expansion of infiltrating T cells.

Neo-antigens are produced with increasing mutation load, and in their study Johnson's team focused on hybrid capture–based NGS, for which they collaborated with Foundation Medicine and Adaptive Biotechnologies for sample analysis. The goal was to study a smaller portion of the genome to get an accurate surrogate for mutation load.

Mutational load captured following hybrid capture–based NGS of coding sequences 236 to 315 were correlated with clinical outcomes and compared with whole genome sequencing, Johnson said. Patients were divided into an initial cohort (median age 55 years) and a validation cohort (median age 62 years). Patients were treated with either nivolumab, pembrolizumab, or atezolizumab, and prior lines of treatment could include BRAF inhibitor, ipilimumab, or chemotherapy.[3]

Among patients in the initial cohort (n = 32) who responded to anti-PD-1 and anti–PD-L1 agents, higher mutation load was significantly greater in responders compared with nonresponders—responders had a median mutation load of 45.6 mutations/MB, compared with 3.9 mutations/MB among nonresponders. In the validation cohort (n = 33), responders had a median mutation load of 37.1 mutations/MB, compared with 12.8 mutations/MB among nonresponders.

Johnson and his team evaluated specific gene mutations in the patient samples and observed that more number of responders had mutations in NF1, LRP1B, and BRCA2, compared with nonresponders. Significantly, similar to what Diaz presented for CRC, patients with a high mutation load had greater PFS and OS compared with patients with low- or medium mutation load.

"Is mutation load a positive prognostic feature?" Johnson asked. Based on their findings, Johnson proposed a potential model for treatment, derived from the mutation load of patients. According to the model, in patients with metastatic melanoma, a high mutation load should be the cue for treatment with anti–PD-1 monotherapy, and low- or intermediate mutation load patients should be treated with combinations such as ipilimumab plus nivolumab. **EBO**

REFERENCES

1. Dangi-Garimella S. Predictive biomarkers present promise in immuno-oncology. *The American Journal of Managed Care* website. http://www.ajmc.com/conferences/asco2015/predictive-biomarkers-present-promise-in-immuno-oncology. Published May 31, 2015. Accessed June 20, 2016.
2. Le DT, Uram JN, Wang H, et al. Programmed death-1 blockade in mismatch repair deficient colorectal cancer. *J Clin Oncol*. 2016;34 (suppl; abstract 103).
3. Johnson DB, Frampton GM, Rioth MJ, et al. Hybrid capture-based next-generation sequencing (HC NGS) in melanoma to identify markers of response to anti-PD-1/PD-L1. *J Clin Oncol*. 2016;34 (suppl; abstract 105).

HEALTHCARE POLICY

Lessons to Learn From the NICE Cancer Care Model

SURABHI DANGI-GARIMELLA, PHD


ROGERS


KERR

On the first day of the annual meeting of the American Society of Clinical Oncology, held June 3-7, 2016, in Chicago, IL, healthcare experts from the United States, Canada, and the United Kingdom, compared and contrasted the care models that are widely adopted in each nation. Placing a significant emphasis on reviewing the value of cancer care, panelists discussed how the National Institute for Health and Care Excellence (NICE) in the United Kingdom, and the Canadian healthcare model, seek to optimize the cost and value of cancer care. Panelists also identified opportunities for constructive interventions that could help fill existing gaps in the US healthcare system.

United States

Susan Rogers, MD, FACP, Stroger Hospital of Cook County, Physicians for a National Health Program, introduced the US healthcare system during her talk, Perverse Incentives and Broken Markets: How Did We Get Here and How Do We Correct It?

Rogers posed the question, "Why do we need a single payer?" But, before trying to answer that question, she explained why health insurance is so important. Rogers said that insuring against health:

- Protects financial assets
- Improves access to care
- Protects health

"The United States has 5 health delivery systems," Rogers said, listing them as:

1. Medicare
2. Medicaid
3. Private insurance offered to workers where they have to contribute to the premium
4. Healthcare for Native Americans, vets, and the military, provided and delivered by the government (socialized medicine)
5. Healthcare for the uninsured

"We are spending a lot of money on healthcare. The US public spending per capita for health is greater than the total spending in other nations," Rogers said, with accompanying slides showing that US spends significantly greater than the highest amount spent by other developing countries. She emphasized that the increased spending does not guarantee improved outcomes, such as an improvement in the infant mortality rate or improved longevity.

So how can we improve access to better healthcare? Rogers pointed out that employment alone does not guarantee health benefits because a lot of employers prefer part-time employees, who then do not qualify for health benefits. With Medicaid expansion following the Affordable Care Act (ACA), there was hope that disparities in access to healthcare would be addressed. But it was not to be. "If half the physicians are not participating in Medicaid managed care plans, how can patients access care with those doctors?" Rogers asked. Despite the provisions within ACA, the Congressional Budget Office has estimated that 30 million will remain uninsured in 2016 and the number will hover around 29 million until 2019.[1]

The ACA has not really helped the US population, Rogers said, because a standard benefits package was not developed under the ACA—so many services are not covered by the health plan till the enrollee meets the target deductible amount. Copays and coinsurance were eliminated for enrollees, but only for preventive services and annual wellness visits. "ACA makes underinsurance the norm," she said. "With the average deductibles steadily rising, from $300 in 2006 to $1077 in 2015, medical bankruptcies are significantly higher, especially among cancer patients," Rogers pointed out.

VOTING FOR A SINGLE-PAYER SYSTEM

Rogers is a big proponent of a single-payer system—she believes it presents several advantages that private plans do not offer. When a person seeks care at a site, some of the providers may not be in network, and so when the patients use those services, they may end up being very expensive, according to Rogers. "A single-payer system, on the other hand, will remove provider restrictions and improve access and choice for all."

While it might cost more to cover everyone (she showed an estimate of $243 billion), a single-payer system can be kept funded by eliminating discrepancies in service costs, reducing administrative costs, reducing drug prices via negotiations, and by introducing a payroll tax instead of a deduction.

Belgium was the first developed country to introduce a government-backed universal health insurance, back in 1945. Subsequently, several countries in Europe, and in Asia, followed suit.

"ACA is based on private insurance and will not be able to solve patient access issues," Rogers said. "A single payer will be the only insurance plan that can allow cost control, provide access, and provide better choice."

United Kingdom

David J. Kerr, MD, PhD, University of Oxford, who chaired the panel, serves on the advisory board of the National Health Services, Scotland. Kerr began his talk, Across the Pond: Learning from the U.K. Experience, by sharing the definition of "value" by Michael Porter, MD, which says that value should be defined around the consumer, not the supplier. Patient performance, not the volume of services provided, is important when considering the value of a service.

Kerr listed several enemies of better value cancer care:

- Unwarranted variation
- Inequalities in care
- Inadequate focus on prevention
- Waste of resources
- Patient harm even with high-quality care

From the societal perspective, "We have an increase in demand and increased burden, with an ageing population. Each medical advance is hailed as 'breakthrough,' which raises the hope of patients and caregivers," Kerr said. He added that our current health models have a demand of transparency and openness from patients and caregivers, but there have been financial constraints imposed by global recession.

Additionally, healthcare spending is burdened with treating conditions that were previously untreatable, and patients who were previously untreatable. Expensive treatments, Kerr emphasized, are a sum total of expensive drugs, expensive services such as complicated surgery, expensive imaging, and expensive tests.

Kerr explained that the National Institute for Health and Care Excellence (NICE) guides clinical practice (pathways of care), public health, and HTA decisions. NICE, Kerr said, abides by the following core values:

- Input from the public, advocacy groups, and caregivers
- Transparent process and decision making
- Consultation
- Regular review

Outcomes data that NICE considers when making decisions include cost-benefit, clinical benefit, cost-effectiveness ratio, and health benefit (measured in terms of quality-adjusted life-years or QALY).

Kerr then highlighted several approaches that NICE has proposed to curb the rising cost of cancer drugs:

- Reduce clinical trial costs by 40% to 60% without reducing their quality.
- Greater use of adaptive design techniques to reduce trial duration and the number of patients needed.
- Data requirements by regulatory bodies should be challenged by oncologists and patient advocacy groups.
- Drug costs should be challenged by oncologists and patient advocacy groups.

Canada

North of the Border: Harnessing Market Forces, Deregulation, and Consumer Choice in Canada, was the title of the presentation by Ralph Wong, MD, FRCPC, CancerCare Manitoba. Wong explained what works and what does not with the publicly funded single-payer system in Canada. "The Canada Health Act of 1984 says that all insured are entitled to the same level of healthcare," Wong shared, adding that the outcome is debatable. "Individual provinces and territories in Canada have their own agenda, which can result in unequal distribution of healthcare," he said.

The drug approval process can take as much as 2 years in Canada, Wong said, adding that Health Canada needs much longer than the FDA to approve a drug, "although we are at par with the EMA [European Medicines Agency]." Wong said the fact that Canada's market is much smaller is a likely reason that drug developers wait to seek approval.

HEALTH TECHNOLOGY ASSESSMENT IN CANADA

The pan-Canadian Oncology Drug Review (pCODR), established in 2010, conducts the health technology assessment (HTA) for Canada. pCODR offers manufacturers and tumor groups the option of a review before submitting for a Notice of Compliance (NOC) with Health Canada. The HTA review and the NOC can run in parallel.

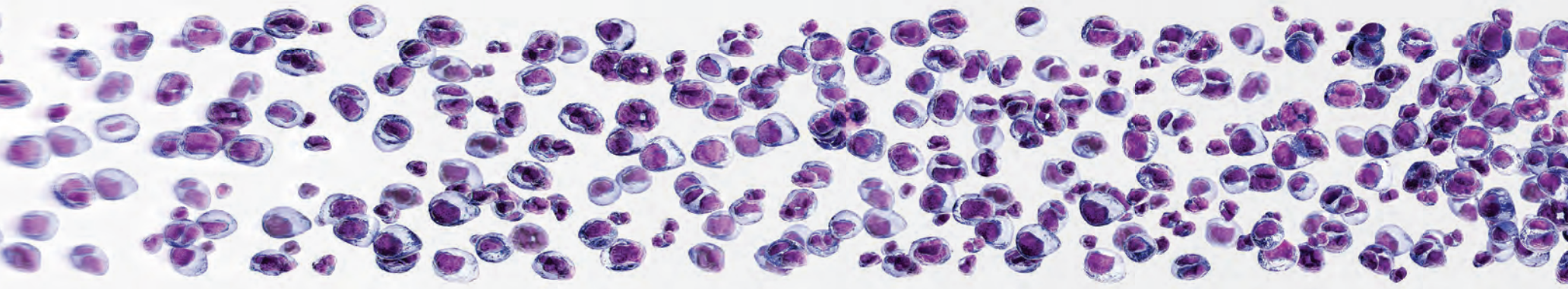
pCODR has been documented to recommend 65% of submissions, 14% may or may not be approved, and 21% are usually denied funding. "It's important to note, however, that oral medications do stand a chance of being paid for by a private insurer. Intravenous infusions could also be funded by private insurers sometimes," Wong said.

(continued on **SP364**)

> **"ACA makes underinsurance the norm. With the average deductibles steadily rising, from $300 in 2006 to $1077 in 2015, medical bankruptcies are significantly higher, especially among cancer patients."**
> —SUSAN ROGERS, MD, FACP

> **Expensive treatments, Kerr emphasized, are a sum total of expensive drugs, expensive services such as complicated surgery, expensive imaging, and expensive tests.**

When multiple myeloma relapses...



Superior PFS and deeper response shown in the ASPIRE* study

26.3 MONTHS

Median PFS†

- 26.3 months for KRd vs 17.6 months for Rd, two-sided $P = 0.0001$[1]

>3X INCREASED

Complete response or better (≥ CR)

- 32% for KRd vs 9% for Rd[1]

*ASPIRE = C**A**rfilzomib, Lenalidomide, and Dexametha**S**one versus Lenalidomide and Dexamethasone for the treatment of P**a**t**I**ents with **R**elapsed Multiple My**E**loma.

INDICATION

- KYPROLIS® (carfilzomib) is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

IMPORTANT SAFETY INFORMATION

Cardiac Toxicities: New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of KYPROLIS. Some events occurred in patients with normal baseline ventricular function. Death due to cardiac arrest has occurred within one day of KYPROLIS administration.

- Monitor patients for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold KYPROLIS for Grade 3 or 4 cardiac adverse events until recovery, and consider whether to restart KYPROLIS at 1 dose level reduction based on a benefit/risk assessment.
- While adequate hydration is required prior to each dose in Cycle 1, monitor all patients for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate in patients with baseline cardiac failure or who are at risk for cardiac failure.
- Patients ≥ 75 years, the risk of cardiac failure is increased. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias may be at greater risk for cardiac complications and should have a comprehensive medical assessment (including blood pressure and fluid management) prior to starting treatment with KYPROLIS and remain under close follow-up.

Acute Renal Failure: Cases of acute renal failure and renal insufficiency adverse events (including renal failure) have occurred in patients receiving KYPROLIS. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received KYPROLIS monotherapy. Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

Tumor Lysis Syndrome: Cases of Tumor Lysis Syndrome (TLS), including fatal outcomes, have occurred in patients receiving KYPROLIS. Patients with multiple myeloma and a high tumor burden should be considered at greater risk for TLS. Adequate hydration is required prior to each dose in Cycle 1, and in subsequent cycles as needed. Consider uric acid lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly. Withhold KYPROLIS until TLS is resolved.

Pulmonary Toxicity: Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in patients receiving KYPROLIS. Some events have been fatal. In the event of drug-induced pulmonary toxicity, discontinue KYPROLIS.

Pulmonary Hypertension: Pulmonary arterial hypertension (PAH) was reported in patients treated with KYPROLIS. Evaluate with cardiac imaging and/or other tests as indicated. Withhold KYPROLIS for PAH until resolved or returned to baseline and consider whether to restart KYPROLIS based on a benefit/risk assessment.

Dyspnea: Dyspnea was reported in patients treated with KYPROLIS. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop KYPROLIS for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart KYPROLIS based on a benefit/risk assessment.

Hypertension: Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with KYPROLIS. Some of these events have been fatal. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold KYPROLIS and evaluate. Consider whether to restart KYPROLIS based on a benefit/risk assessment.

Venous Thrombosis: Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with KYPROLIS. Thromboprophylaxis is recommended for patients being treated with the combination of KYPROLIS with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.

- Patients using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment with KYPROLIS in combination with dexamethasone or lenalidomide plus dexamethasone.

Infusion Reactions: Infusion reactions, including life-threatening reactions, have occurred in patients receiving KYPROLIS. Symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of KYPROLIS. Premedicate with dexamethasone to reduce the incidence and severity of infusion reactions. Inform patients of the risk and of symptoms of an infusion reaction and to contact a physician immediately if they occur.

Thrombocytopenia: KYPROLIS causes thrombocytopenia with recovery to baseline platelet count usually by the start of the next cycle. Thrombocytopenia was reported in patients receiving KYPROLIS. Monitor platelet counts frequently during treatment with KYPROLIS. Reduce or withhold dose as appropriate.

Hepatic Toxicity and Hepatic Failure: Cases of hepatic failure, including fatal cases, have been reported during treatment with KYPROLIS. KYPROLIS can cause increased serum transaminases. Monitor liver enzymes regularly regardless of baseline values. Reduce or withhold dose as appropriate.

Thrombotic Microangiopathy: Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), including fatal outcome have occurred in patients receiving KYPROLIS. Monitor for signs and symptoms of TTP/HUS. Discontinue KYPROLIS if diagnosis is suspected. If the diagnosis of TTP/HUS is excluded, KYPROLIS may be restarted. The safety of reinitiating KYPROLIS therapy in patients previously experiencing TTP/HUS is not known.

Posterior Reversible Encephalopathy Syndrome (PRES): Cases of PRES have occurred in patients receiving KYPROLIS. PRES was formerly known as Reversible Posterior Leukoencephalopathy Syndrome. Consider a neuro-radiological imaging (MRI) for onset of visual or neurological symptoms. Discontinue KYPROLIS if PRES is suspected and evaluate. The safety of reinitiating KYPROLIS therapy in patients previously experiencing PRES is not known.

Embryo-fetal Toxicity: KYPROLIS can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals.

- Females of reproductive potential should be advised to avoid becoming pregnant while being treated with KYPROLIS. Males of reproductive potential should be advised to avoid fathering a child while being treated with KYPROLIS. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the fetus.

ADVERSE REACTIONS

- The most common adverse reactions occurring in at least 20% of patients treated with KYPROLIS in the combination therapy trials: anemia, neutropenia, diarrhea, dyspnea, fatigue, thrombocytopenia, pyrexia, insomnia, muscle spasm, cough, upper respiratory tract infection, hypokalemia.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.

Please see Brief Summary of full Prescribing Information on adjacent pages.

ASPIRE: A phase 3, randomized, open-label, multicenter superiority study evaluated KYPROLIS in combination with lenalidomide and dexamethasone (KRd) vs lenalidomide and dexamethasone (Rd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 prior lines of therapy. 792 patients were randomized in a 1:1 ratio (396 patients to KRd, 396 to Rd). Patients received their randomized study treatment in 28-day cycles until disease progression or unacceptable toxicity occurred. KYPROLIS was discontinued at 18 cycles unless disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Select secondary endpoints included overall survival, overall response rate (ORR), and duration of response.[1,2]

References: 1. KYPROLIS [prescribing information]. Thousand Oaks, CA: Onyx Pharmaceuticals, Inc., an Amgen Inc. subsidiary; 2016. **2.** Stewart AK, Rajkumar SV, Dimopoulos MA, et al; for the ASPIRE Investigators. *N Engl J Med*. 2015;372:142-152.

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USA-171-120751 February 2016 Printed in USA

Kyprolis™ (carfilzomib) for Injection

KYPROLIS® (carfilzomib) for injection, for intravenous use
Brief Summary of Prescribing Information.
Please see the KYPROLIS package insert for full prescribing information.

1. INDICATIONS AND USAGE

- Kyprolis is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.
- Kyprolis is indicated as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.

2. DOSAGE AND ADMINISTRATION

2.1 Administration Precautions

Hydration - Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high risk of tumor lysis syndrome or renal toxicity and following the administration of Kyprolis with both oral and intravenous (IV) fluids, if needed. **Electrolyte monitoring -** Monitor serum potassium levels regularly during treatment with Kyprolis. **Premedications -** Premedicate with the recommended dose of dexamethasone for monotherapy or the recommended dose if on combination therapy. Reinstate dexamethasone premedication if these symptoms occur during subsequent cycles. **Administration -** Infuse over 10 or 30 minutes depending on the Kyprolis dose regimen. Do not administer as a bolus. Flush the IV line with normal saline or 5% dextrose injection, USP, immediately before and after Kyprolis administration. Do not mix Kyprolis with or administer as an infusion with other medicinal products. **Thromboprophylaxis -** Thromboprophylaxis is recommend for patients being treated with the combination of Kyprolis with dexamethasone or with lenalidomide plus dexamethasone. **Infection Prophylaxis -** Consider antiviral prophylaxis for patients being treated with Kyprolis to decrease the risk of herpes zoster reactivation.

5. WARNINGS AND PRECAUTIONS

5.1 Cardiac Toxicities

New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of Kyprolis. Some events occurred in patients with normal baseline ventricular function. In clinical studies with Kyprolis, these events occurred throughout the course of Kyprolis therapy. Death due to cardiac arrest has occurred within one day of Kyprolis administration. In a randomized, open-label, multicenter trial evaluating Kyprolis in combination with lenalidomide and dexamethasone (KRd) versus lenalidomide/dexamethasone (Rd), the incidence of cardiac failure events was 6% in the KRd arm versus 4% in the Rd arm. In a randomized, open-label, multicenter trial of Kyprolis plus dexamethasone (Kd) versus bortezomib plus dexamethasone (Vd), the incidence of cardiac failure events was 8% in the Kd arm versus 3% in the Vd arm.

Monitor patients for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold Kyprolis for Grade 3 or 4 cardiac adverse events until recovery, consider whether to restart Kyprolis at 1 dose level reduction based on a benefit/risk assessment.

While adequate hydration is required prior to each dose in Cycle 1, all patients should also be monitored for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate in patients with baseline cardiac failure or who are at risk for cardiac failure.

In patients ≥ 75 years of age, the risk of cardiac failure is increased compared to patients < 75 years of age. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications and should have a comprehensive medical assessment (including blood pressure and fluid management) prior to starting treatment with Kyprolis and remain under close follow-up.

5.2 Acute Renal Failure

Cases of acute renal failure have occurred in patients receiving Kyprolis. Renal insufficiency adverse events (including renal failure) have occurred in approximately 10% of patients treated with Kyprolis. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received Kyprolis monotherapy. This risk was greater in patients with a baseline reduced estimated creatinine clearance (calculated using Cockcroft and Gault equation). Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

5.3 Tumor Lysis Syndrome

Cases of tumor lysis syndrome (TLS), including fatal outcomes, have been reported in patients who received Kyprolis. Patients with multiple myeloma and a high tumor burden should be considered to be at greater risk for TLS. Ensure that patients are well hydrated before administration of Kyprolis in Cycle 1, and in subsequent cycles as needed. Consider uric acid-lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly, including interruption of Kyprolis until TLS is resolved.

5.4 Pulmonary Toxicity

Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in less than 1% of patients receiving Kyprolis. Some events have been fatal. In the event of drug-induced pulmonary toxicity, discontinue Kyprolis.

5.5 Pulmonary Hypertension

Pulmonary arterial hypertension was reported in approximately 1% of patients treated with Kyprolis and was Grade 3 or greater in less than 1% of patients. Evaluate with cardiac imaging and/or other tests as indicated. Withhold Kyprolis for pulmonary hypertension until resolved or returned to baseline, and consider whether to restart Kyprolis based on a benefit/risk assessment.

5.6 Dyspnea

Dyspnea was reported in 28% of patients treated with Kyprolis and was Grade 3 or greater in 4% of patients. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop Kyprolis for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart Kyprolis based on a benefit/risk assessment.

5.7 Hypertension

Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with Kyprolis. In a randomized, open-label, multicenter trial evaluating Kyprolis in combination with KRd versus Rd, the incidence of hypertension events was 16% in the KRd arm versus 8% in the Rd arm. In a randomized, open-label, multicenter trial of Kd versus Vd, the incidence of hypertension events was 26% in the Kd arm versus 10% in the Vd arm. Some of these events have been fatal. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold Kyprolis and evaluate. Consider whether to restart Kyprolis based on a benefit/risk assessment.

5.8 Venous Thrombosis

Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with Kyprolis. In a randomized, open-label, multicenter trial evaluating KRd versus Rd (with thromboprophylaxis used in both arms), the incidence of venous thromboembolic events in the first 12 cycles was 13% in the KRd arm versus 6% in the Rd arm. In a randomized, open-label, multicenter trial of Kd versus Vd, the incidence of venous thromboembolic events in months 1–6 was 9% in the Kd arm versus 2% in the Vd arm. With Kyprolis monotherapy, the incidence of venous thromboembolic events was 2%.

Thromboprophylaxis is recommended for patients being treated with the combination of Kyprolis with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.

Patients using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment with Kyprolis in combination with dexamethasone or lenalidomide plus dexamethasone.

5.9 Infusion Reactions

Infusion reactions, including life-threatening reactions, have occurred in patients receiving Kyprolis. Symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of Kyprolis. Administer dexamethasone prior to Kyprolis to reduce the incidence and severity of infusion reactions. Inform patients of the risk and of symptoms and to contact a physician immediately if symptoms of an infusion reaction occur.

5.10 Thrombocytopenia

Kyprolis causes thrombocytopenia with platelet nadirs observed between Day 8 and Day 15 of each 28-day cycle, with recovery to baseline platelet count usually by the start of the next cycle. Thrombocytopenia was reported in approximately 40% of patients in clinical trials with Kyprolis. Monitor platelet counts frequently during treatment with Kyprolis. Reduce or withhold dose as appropriate.

5.11 Hepatic Toxicity and Hepatic Failure

Cases of hepatic failure, including fatal cases, have been reported (< 1%) during treatment with Kyprolis. Kyprolis can cause increased serum transaminases. Monitor liver enzymes regularly, regardless of baseline values. Reduce or withhold dose as appropriate.

5.12 Thrombotic Microangiopathy

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received Kyprolis. Some of these events have been fatal. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop Kyprolis and evaluate. If the diagnosis of TTP/HUS is excluded, Kyprolis may be restarted. The safety of reinitiating Kyprolis therapy in patients previously experiencing TTP/HUS is not known.

5.13 Posterior Reversible Encephalopathy Syndrome

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving Kyprolis. PRES, formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS), is a neurological disorder which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension, and the diagnosis is confirmed by neuro-radiological imaging (MRI). Discontinue Kyprolis if PRES is suspected and evaluate. The safety of reinitiating Kyprolis therapy in patients previously experiencing PRES is not known.

5.14 Embryo-Fetal Toxicity

Kyprolis can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using Kyprolis.

Females of reproductive potential should be advised to avoid becoming pregnant while being treated with Kyprolis. Males of reproductive potential should be advised to avoid fathering a child while being treated with Kyprolis. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the fetus.

6. ADVERSE REACTIONS

The following adverse reactions have been discussed above and can be found in the Warning and Precautions section of the prescribing information. They include Cardiac Toxicities, Acute Renal Failure, TLS, Pulmonary Toxicity, Pulmonary Hypertension, Dyspnea, Hypertension, Venous Thrombosis, Infusion Reactions, Thrombocytopenia, Hepatic Toxicity and Hepatic Failure, Thrombotic Microangiopathy, and PRES.

6.1 Clinical Trials Experience

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

Safety Experience with Kyprolis in Combination with Lenalidomide and Dexamethasone in Patients with Multiple Myeloma

The safety of Kyprolis in combination with lenalidomide and dexamethasone (KRd) was evaluated in an open-label randomized study in patients with relapsed multiple myeloma. The median number of cycles initiated was 22 cycles for the KRd arm and 14 cycles for the Rd arm.

Deaths due to adverse reactions within 30 days of the last dose of any therapy in the KRd arm occurred in 27/392 (7%) patients compared with 27/389 (7%) patients who died due to adverse reactions within 30 days of the last dose of any Rd therapy. The most common cause of deaths occurring in patients (%) in the two arms (KRd versus Rd) included cardiac 10 (3%) versus 7 (2%), infection 9 (2%) versus 10 (3%), renal 0 (0%) versus 1 (< 1%), and other adverse reactions 9 (2%) versus 10 (3%). Serious adverse reactions were reported in 60% of the patients in the KRd arm and 54% of the patients in the Rd arm. The most common serious adverse reactions reported in the KRd arm as compared with the Rd arm were pneumonia (14% vs. 11%), respiratory tract infection (4% vs. 1.5%), pyrexia (4% vs. 2%), and pulmonary embolism (3% vs. 2%). Discontinuation due to any adverse reaction occurred in 26% in the KRd arm versus 25% in the Rd arm. Adverse reactions leading to discontinuation of Kyprolis occurred in 12% of patients and the most common reactions included pneumonia (1%), myocardial infarction (0.8%), and upper respiratory tract infection (0.8%).

Most Common Adverse Reactions (≥ 10% in the KRd Arm) Occurring in Cycles 1–12 (20/27 mg/m² Regimen in Combination with Lenalidomide and Dexamethasone)

	KRd Arm (N = 392), n (%)		Rd Arm (N = 389), n (%)	
Adverse Reactions by Body System	**Any Grade**	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**
Blood and Lymphatic System Disorders				
Anemia	138 (35)	53 (14)	127 (33)	47 (12)
Neutropenia	124 (32)	104 (27)	115 (30)	89 (23)
Thrombocytopenia	100 (26)	58 (15)	75 (19)	39 (10)
Gastrointestinal Disorders				
Diarrhea	115 (29)	7 (2)	105 (27)	12 (3)
Constipation	68 (17)	0	53 (14)	1 (0)
Nausea	60 (15)	1 (0)	39 (10)	3 (1)
General Disorders and Administration Site Conditions				
Fatigue	109 (28)	21 (5)	104 (27)	20 (5)
Pyrexia	93 (24)	5 (1)	64 (17)	1 (0)
Edema peripheral	63 (16)	2 (1)	57 (15)	2 (1)
Asthenia	53 (14)	11 (3)	46 (12)	7 (2)
Infections and Infestations				
Upper respiratory tract infection	85 (22)	7 (2)	52 (13)	3 (1)
Nasopharyngitis	63 (16)	0	43 (11)	0
Bronchitis	54 (14)	5 (1)	39 (10)	2 (1)
Pneumonia[a]	54 (14)	35 (9)	43 (11)	27 (7)
Metabolism and Nutrition Disorders				
Hypokalemia	78 (20)	22 (6)	35 (9)	12 (3)
Hypocalcemia	55 (14)	10 (3)	39 (10)	5 (1)
Hyperglycemia	43 (11)	18 (5)	33 (9)	15 (4)

Musculoskeletal and Connective Tissue Disorders				
Muscle spasms	88 (22)	3 (1)	73 (19)	3 (1)
Nervous System Disorders				
Peripheral neuropathies[b]	43 (11)	7 (2)	37 (10)	4 (1)
Psychiatric Disorders				
Insomnia	63 (16)	6 (2)	50 (13)	8 (2)
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	85 (22)	1 (0)	46 (12)	0
Dyspnea[c]	70 (18)	9 (2)	58 (15)	6 (2)
Skin and Subcutaneous Tissue Disorders				
Rash	45 (12)	5 (1)	53 (14)	5 (1)
Vascular Disorders				
Embolic and thrombotic events, venous[d]	49 (13)	16 (4)	22 (6)	9 (2)
Hypertension[e]	41 (11)	12 (3)	15 (4)	4 (1)

KRd = Kyprolis, lenalidomide, and low-dose dexamethasone; Rd = lenalidomide and low-dose dexamethasone.

[a] Pneumonia includes pneumonia and bronchopneumonia.

[b] Peripheral neuropathies includes peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.

[c] Dyspnea includes dyspnea and dyspnea exertional.

[d] Embolic and thrombotic events, venous include deep vein thrombosis, pulmonary embolism, thrombophlebitis superficial, thrombophlebitis, venous thrombosis limb, post thrombotic syndrome, venous thrombosis.

[e] Hypertension includes hypertension, hypertensive crisis.

Grade 3–4 Laboratory Abnormalities (≥10%) in Cycles 1–12 (20/27 mg/m^2 Regimen in Combination with Lenalidomide and Dexamethasone)

Laboratory Abnormality	KRd (N = 392), n (%)	Rd (N = 389), n (%)
Decreased lymphocytes	182 (46)	119 (31)
Decreased absolute neutrophil count	152 (39)	140 (36)
Decreased phosphorus	122 (31)	106 (27)
Decreased platelets	101 (26)	59 (15)
Decreased total white blood cell count	97 (25)	71 (18)
Decreased hemoglobin	58 (15)	68 (18)
Decreased potassium	41 (11)	23 (6)

KRd = Kyprolis, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone.

Safety Experience with Kyprolis in Combination with Dexamethasone in Patients with Multiple Myeloma

The safety of Kyprolis in combination with dexamethasone was evaluated in an open-label, randomized trial of patients with relapsed multiple myeloma. Patients received treatment for a median duration of 40 weeks in the Kyprolis/dexamethasone (Kd) arm and 27 weeks in the bortezomib/dexamethasone (Vd) arm.

Deaths due to adverse reactions within 30 days of last study treatment occurred in 22/463 (5%) patients in the Kd arm and 21/456 (5%) patients in the Vd arm. The causes of death occurring in patients (%) in the two arms (Kd vs. Vd) included cardiac 7 (2%) versus 5 (1%), infections 5 (1%) versus 8 (2%), disease progression 6 (1%) versus 4 (1%), pulmonary 3 (1%) versus 2 (< 1%), renal 1 (< 1%) versus 0 (0%), and other adverse events 2 (< 1%) versus 2 (< 1%). Serious adverse reactions were reported in 48% of the patients in the Kd arm and 36% of the patients in the Vd arm. In both treatment arms, pneumonia was the most commonly reported serious adverse reaction (6% vs. 9%). Discontinuation due to any adverse reaction occurred in 20% in the Kd arm versus 21% in the Vd arm. The most common reaction leading to discontinuation was cardiac failure in the Kd arm (n = 6, 1.3%) and peripheral neuropathy in the Vd arm (n = 19, 4.2%).

There were 274 (70%) patients in the KRd arm who received treatment beyond Cycle 12. There were no new clinically relevant AEs that emerged in the later treatment cycles.

Most Common Adverse Reactions (≥ 10% in the Kd Arm) Occurring in Months 1–6 (20/56 mg/m^2 Regimen in Combination with Dexamethasone)

	Kd (N = 463), n (%)		Vd (N = 456), n (%)	
Adverse Reaction by Body System	**Any Grade**	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**
Blood and Lymphatic System Disorders				
Anemia	160 (35)	57 (12)	112 (25)	43 (9)
Thrombocytopenia[a]	127 (27)	46 (10)	112 (25)	65 (14)
Gastrointestinal Disorders				
Diarrhea	111 (24)	14 (3)	150 (33)	26 (6)
Nausea	69 (15)	4 (1)	66 (15)	3 (1)
Constipation	58 (13)	1 (0)	109 (24)	6 (1)
Vomiting	45 (10)	5 (1)	32 (7)	3 (1)
General Disorders and Administration Site Conditions				
Fatigue	112 (24)	13 (3)	124 (27)	25 (6)
Pyrexia	102 (22)	9 (2)	52 (11)	3 (1)
Peripheral edema	75 (16)	3 (1)	73 (16)	3 (1)
Asthenia	71 (15)	9 (2)	66 (14)	13 (3)
Infections and Infestations				
Upper respiratory tract infection	66 (14)	4 (1)	54 (12)	3 (1)
Bronchitis	54 (12)	5 (1)	26 (6)	2 (0)
Nasopharyngitis	45 (10)	0 (0)	42 (9)	1 (0)
Musculoskeletal and Connective Tissue Disorders				
Muscle spasms	66 (14)	1 (0)	22 (5)	3 (1)
Back pain	58 (13)	7 (2)	60 (13)	8 (2)
Nervous System Disorders				
Headache	68 (15)	4 (1)	38 (8)	2 (0)
Peripheral neuropathies[b]	54 (12)	7 (2)	167 (37)	23 (5)
Psychiatric Disorders				
Insomnia	103 (22)	5 (1)	113 (25)	10 (2)
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea[c]	123 (27)	23 (5)	66 (15)	8 (2)
Cough	77 (17)	0 (0)	55 (12)	1 (0)
Vascular Disorders				
Hypertension[d]	80 (17)	29 (6)	33 (7)	12 (3)

Kd = Kyprolis and dexamethasone; Vd = bortezomib and dexamethasone.

[a] Thrombocytopenia includes platelet count decreased and thrombocytopenia.

[b] Peripheral neuropathies include peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.

[c] Dyspnea includes dyspnea and dyspnea exertional.

[d] Hypertension includes hypertension, hypertensive crisis, and hypertensive emergency.

The event rate of ≥ Grade 2 peripheral neuropathy in the Kd arm was 6% (95% CI: 4, 8) versus 32% (95% CI: 28, 36) in the Vd arm.

Grade 3 and higher adverse reactions that occurred during Cycles 1-12 with a substantial difference (≥ 2%) between the two arms were neutropenia, thrombocytopenia, hypokalemia, and hypophosphatemia.

6.2 Postmarketing Experience

The following additional adverse reactions were reported in the post-marketing experience with Kyprolis. 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: hemolytic uremic syndrome (HUS), gastrointestinal perforation, pericarditis.

7. DRUG INTERACTIONS

Carfilzomib is primarily metabolized via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers. Carfilzomib is not expected to influence exposure of other drugs.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Kyprolis can cause fetal harm based on findings from animal studies and the drug's mechanism of action. There are no adequate and well-controlled studies in pregnant women using Kyprolis.

Females of reproductive potential should be advised to avoid becoming pregnant while being treated with Kyprolis. Males of reproductive potential should be advised to avoid fathering a child while being treated with Kyprolis. Consider the benefits and risks of Kyprolis and possible risks to the fetus when prescribing Kyprolis to a pregnant woman. If Kyprolis is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of Kyprolis in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Kyprolis and any potential adverse effects on the breastfed infant from Kyprolis or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Kyprolis can cause fetal harm. Advise female patients of reproductive potential to use effective contraceptive measures or abstain from sexual activity to prevent pregnancy during treatment with Kyprolis and for at least 30 days following completion of therapy. Advise male patients of reproductive potential to use effective contraceptive measures or abstain from sexual activity to prevent pregnancy during treatment with Kyprolis and for at least 90 days following completion of therapy.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of 598 patients in clinical studies of Kyprolis monotherapy dosed at 20/27 mg/m^2 by up to 10-minute infusion, 49% were 65 and over, while 16% were 75 and over. The incidence of serious adverse events was 44% in patients < 65 years of age, 55% in patients 65 to 74 years of age, and 56% in patients ≥ 75 years of age. In a single-arm, multicenter clinical trial of Kyprolis monotherapy dosed at 20/27 mg/m^2 (N = 266), no overall differences in effectiveness were observed between older and younger patients.

Of 392 patients treated with Kyprolis in combination with lenalidomide and dexamethasone, 47% were 65 and over and 11% were 75 years and over. The incidence of serious adverse events was 50% in patients < 65 years of age, 70% in patients 65 to 74 years of age, and 74% in patients ≥ 75 years of age. No overall differences in effectiveness were observed between older and younger patients.

Of 463 patients treated with Kyprolis dosed at 20/56 mg/m^2 by 30-minute infusion in combination with dexamethasone, 52% were 65 and over and 17% were 75 and over. The incidence of serious adverse events was 44% in patients < 65 years of age, 50% in patients 65 to 74 years of age, and 57% in patients ≥ 75 years of age. No overall differences in effectiveness were observed between older and younger patients.

8.6 Renal Impairment

No starting dose adjustment is required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis. The pharmacokinetics and safety of Kyprolis were evaluated in a Phase 2 trial in patients with normal renal function and those with mild, moderate, and severe renal impairment and patients on chronic dialysis. In this study, the pharmacokinetics of Kyprolis was not influenced by the degree of baseline renal impairment, including the patients on dialysis. Since dialysis clearance of Kyprolis concentrations has not been studied, the drug should be administered after the dialysis procedure.

10. OVERDOSAGE

Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia, and lymphopenia has been reported following a dose of 200 mg of Kyprolis administered in error.

There is no known specific antidote for Kyprolis overdosage. In the event of overdose, the patient should be monitored, specifically for the side effects and/or adverse reactions listed in the Adverse Reactions section.

The risk information provided here is not comprehensive. The FDA-approved product labeling can be found at www.kyprolis.com or contact Amgen Medical Information at 1-800-772-6436.

This Brief Summary is based on the Kyprolis Prescribing Information v10, 01/16.

U.S. Patent Numbers: http://pat.amgen.com/kyprolis

(continued from **SP359**)

While a significant reduction in the number of days needed for approval has been observed, there is criticism of the overall process. Wong revealed that territorial or provincial governments are ultimate decision makers on when "no means no", but "yes could mean maybe." Additionally, decisions could sometimes be inconsistent.

Following pCODR, the Pan Canadian Pharmaceutical Alliance, or pCPA, then reviews the application for cost-effectiveness via a process that involves negotiations with the drug developer to reduce drug costs. "Only those provinces that participate in the negotiations can claim the discounted rate. But a substantial amount of savings have been noted—C$ 400 million annually for oncology drugs," he said. **EBO**

REFERENCE

1. Congressional Budget Office. Updated estimates of the insurance coverage provisions of the Affordable Care Act. Congressional Budget Office website. https://www.cbo.gov/sites/default/files/114th-congress-2015-2016/reports/49892/49892-breakout-AppendixB.pdf. Accessed June 3, 2016.

Clinical Interpretation of the ASCO Recommendations on Quality and Value

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The American Society of Clinical Oncology (ASCO) recently published an update[1] to the value framework as the next step toward the goal of providing clinicians and patients with a tool for shared decision making. Providing an overview of the framework and ASCO's quality program,[2] the Quality Oncology Practice Initiative (QOPI), was the session Quality and Value: Measuring and Utilizing Both in Your Practice.

Anne C. Chiang, MD, PhD, Yale Cancer Center, provided an overview of the QOPI certification program and explained the impact that this certification could have on the quality of care provided by clinical practices. "The current landscape of oncology is a combination of new immunotherapeutic agents, genomics and precision medicine, technology, and big data," Chiang said, adding that it's a difficult process, trying to balance quality and value of such innovative treatments.

"QOPI is ASCO's signature quality program. Over 1000 practices with 7000 participants have participated in QOPI since 2006," Chiang said, with widespread geographic distribution of the practices that have registered with the program within the United States. Additionally, the QOPI program has crossed international boundaries, and 16 international practices have registered with the program in fall 2015.

So why does QOPI matter? "It's not just about the cost," Chiang said, "but it's also about creating a culture of quality, tools for measurement, benchmarking and standardization opportunities, and driving performance improvement." She provided an example of the Smilow Cancer Center at Yale, which implemented several quality improvement projects, including:

- EPIC, the electronic health record system
- QOPI certification
- An oral chemotherapy initiative
- SRC care center emotional distress project

The cancer center wanted improved standardization across its various sites of care. Following the integration of QOPI practices, a significant improvement in documentation of data was observed at the various clinical sites, Chiang said.

The QOPI certification program also touches various aspects of patient care, and it helps,

- Make the right diagnosis
- Determine the treatment plan
- Communicate with the patients
- Shared decision making

According to Chiang, Smilow is using QOPI to raise the bar for disagreements on pathology referrals, especially when they are conducted at outside labs. "QOPI also provides important tools to comply with MACRA [Medicare Access and CHIP Reauthorization Act], and the Physician Quality Reporting Pathway will help comply with the requirements of MIPS, the merit-based intervention payment system. The QOPI/QCP community is both a quality forum and test ground for evolving solutions to MACRA and future challenges," Chiang said.

ASCO'S VALUE FRAMEWORK

Lowell E. Schnipper, MD, PhD, Beth Israel Deaconess Medical Center, discussed the nuances of the value framework. "The context in which we are entering this space is a new era of treatments that we are utilizing in clinical practice every day," Schnipper said. "Several of these treatments are game changers in care. But these treatments are expensive, and insurance is getting unaffordable for most in the middle-income strata of society."

"We anticipate that the tool we have developed can help patients and providers make treatment decisions. We hope to collaborate with software vendors who can help develop an app for use at the physician-patient interface," Schnipper said. He went on to explain the Net Health Benefit score, or NHB, which has several domains that are regularly used in the clinic, including the biggest domain: clinical benefit. When calculating the NHB, overall survival is valued above progression-free survival, which in turn is above response rate (RR).

Schnipper acknowledged that some of the newer drugs may not have data that compares them with the standard of care, and in such cases RR would be considered. "Bonus points will be awarded to symptom palliation, improved quality of life, and extended survival. Additionally, toxicity subtracts points from NHB," Schnipper said. The task force has developed a separate framework for adjuvant treatments.

Referring to some of the other value frameworks that have been developed, including the National Comprehensive Cancer Center's Evidence Blocks[3] and the Institute of Clinical and Economic Review's value tool,[4] Schnipper said that the focus of ASCO's framework is to have a shared decision-making tool to help patients understand the impact of their treatment on their finances.

Schnipper listed the following open questions:

- How much are we willing to pay and for what amount of gain?
- Is there a role for paying for performance by therapies?

A CASE STUDY

The last presentation was by Steven L. D'Amato, BCOP, RPh, chief executive officer of New England Cancer Specialists, who brought the community oncology perspective to the discussion. Their practice has been a part of the COME HOME project,[5] and they recently also applied for their QOPI recertification.

"QOPI is all about quality," D'Amato said. "It demonstrates commitment to excellence and quality of treatment. As the outpatient setting becomes more prevalent in cancer care, maintaining the quality of care is quite essential."

Explaining some of the nuances of QOPI, he said that there are 5 modules that are evaluated for certification: care at [end of life], symptom/toxicity management, breast cancer, colorectal cancer, and non-small cell lung cancer. "The clinical practice is scored on 26 designated measures, to get an overall quality score, and should meet at least 75% to be certified," D'Amato said.

Site assessment is the second component of certification and is focused on several key areas of patient care, such as staffing, treatment planning and chart documentation, oral adherence, patient education, drug prep, etc.

The goals of QOPI certification, according to D'Amato, are to provide the highest quality care, provide trusted solutions to satisfy the demands for quality activities, 3-year designation of QOPI certification, and to provide good quality care to the local community. What would be the cost to the practice to apply for this quality certification? "It's a combination of monetary value and the staff time required for training and policy/procedure development."

How is this valuable for patients? That remains an open question, according to D'Amato. "Payers are definitely interested in quality information, and provider and staff at the practices do understand the value of this certification," he said.

He added that QOPI certification has definitely improved their own practice at New England Cancer Specialists—it has allowed standardization across their sites and improved their documentation procedures. It also helped them identify areas of focus for each practice.

D'Amato listed several challenges moving forward:

- Communicating quality and value to all
- Can payers be made to compensate for the value added?
- How can certification be made more efficient? Maybe through eQOPI?
- How can the QOPI certification program providers become preferred providers? **EBO**

REFERENCES

1. Dangi-Garimella S. ASCO releases an updated value framework. *The American Journal of Managed Care* website. http://www.ajmc.com/newsroom/asco-releases-an-updated-value-framework. Published May 31, 2016. Accessed June 6, 2016.

2. Dangi-Garimella S. QOPI, the ASCO initiative, improves compliance and promotes quality of patient care. *The American Journal of Managed Care* website. http://www.ajmc.com/journals/evidence-based-oncology/2014/march-2014/qopi-the-asco-initiative-improves-compliance-and-promotes-quality-of-patient-care. Published March 18, 2014.

3. Dangi-Garimella S. Weighing value and patient preference in cancer care: NCCN Evidence Blocks. *The American Journal of Managed Care* website. http://www.ajmc.com/conferences/nccn-2016/weighing-value-and-patient-preference-in-cancer-care-nccn-evidence-blocks-. Published April 1, 2016. Accessed June 6, 2016.

4. Q&A With ICER's Steven D. Pearson. *The American Journal of Managed Care* website. http://www.ajmc.com/journals/evidence-based-oncology/2016/peer-exchange-oncology-stakeholders-summit/qanda-with-icers-steven-d-pearson. Published May 11, 2016. Accessed June 6, 2016.

5. Dangi-Garimella S. An update on the Oncology Medical Home model at the COA conference. *The American Journal of Managed Care* website. http://www.ajmc.com/conferences/coa2016/an-update-on-the-oncology-medical-home-presented-at-the-coa-annual-meeting. Published April 14, 2016. Accessed June 6, 2016.

"The QOPI/QCP community is both a quality forum and test ground for evolving solutions to MACRA and future challenges."

—ANNE C. CHIANG, MD, PHD

Aggressive Cancer Care Widely Used Among Patients at the End of Life

CATE DOUGLASS

Many patients, 65 years or younger, are still receiving aggressive cancer treatment in their final months of life despite ASCO's Choosing Wisely recommendations encouraging symptom-directed palliative care, according to research presented at the 2016 annual meeting of the American Society of Clinical Oncology (ASCO).

Researchers analyzed health claims data between 2007 and 2014 and discovered that 65% of the patients with advanced solid tumors received at least 1 form of aggressive care within the patient's last 30 days of life. Aggressive care in this study[1] was defined as either hospital admission, an intensive care unit (ICU) admission, or an emergency room visit, as well as a chemotherapy or radiation treatment.

The study examined 28,000 patients from 14 different states, all of whom were younger than 65 years, and were diagnosed with either metastatic lung, colorectal, breast, pancreatic, or prostate cancer. The studied group passed away between January 2007 and December 2014.

The research team discovered that the most common form of aggressive care at the patient's end of life was a hospital admission, occurring in 62% to 65% of patients. Less than one-fourth of the study participants died in the hospital instead of at home, which prompted the study authors to suggest that many patients continued to seek aggressive forms of treatments when other options, such as symptom-directed palliative care could have been given at home.

Additionally, the researchers found that only 14% to 18% of patients used hospice care, more patients sought chemotherapy treatment than radiation—24% to 33% and 6% to 21%, respectively—and ICU admissions occurred in nearly 1 in 5 patients. The research project came in response to ASCO's Choosing Wisely recommendations. Lead study author, Ronald C. Chen, MD, MPH, associate professor of radiation oncology at the University of North Carolina in Chapel Hill, and his research team wanted to understand if this guideline helped change the delivery of care, specifically in patients with advanced solid tumors.

In a 2012 issue, ASCO's Choosing Wisely "Top-Five" List of recommendations encouraged symptom-directed palliative care instead of a cancer-directed therapy in patients with advanced solid tumors who are less likely to benefit from the aggressive treatment. Chen explained the importance of determining the appropriate means of care for every patient—a one-size-fits-all approach may not work for every patient nearing end of life.

The most common form of aggressive care at the patient's end of life was a hospital admission, occurring in 62% to 65% of patients. Less than one-fourth of the study participants died in the hospital instead of at home.

"While it can be difficult to predict when a patient is nearing his or her final month of life, we need to do a better job of scaling back disease-directed treatment, and transitioning patients to symptom-directed end-of-life care sooner," Chen said in a statement. "Intensive care at the end of life remains appropriate for some patients. Still, we need more education of both patients and physicians to improve conversations about goals and expectations." He added that while ASCO's recommendations were a critical first step in addressing the use of aggressive care at the end of life, he advised that guidelines alone will not change the widespread practice.

"We need better ways of educating physicians and patients about palliative care and hospice, and we need to make these types of care more accessible," Chen said. **EBO**

REFERENCE

Chen RC, Falchook AD, Tian F, et al. Aggressive care at the end-of-life for younger patients with cancer: Impact of ASCO's Choosing Wisely campaign. *J Clin Oncol*. 2016; 34 (suppl; abstract LBA10033).

HEALTH ECONOMICS

The Value of a 21-Gene Test in Early-Stage Breast Cancer

SURABHI DANGI-GARIMELLA, PHD


KATZ

Can the Oncotype DX Breast Cancer Assay, also known as the 21-gene Recurrence Score (RS) assay, impact recommendation and receipt of chemotherapy in early-stage breast cancer? Does the test also improve patient experience? These were some of the questions posed by researchers from the University of Michigan, with results presented by Steven J. Katz, MD, MPH, during a health policy session at the annual meeting of the American Society of Clinical Oncology.

This particular assay, developed by Genomic Health, is expected to predict disease recurrence and response to chemotherapy in estrogen receptor (ER)–positive, lymph node–negative early-stage breast cancer. According to the company website, the test also predicts the risk of local recurrence in those who have the more common non-invasive form of breast cancer, ductal carcinoma in-situ, commonly referred to as DCIS.

> **"While a majority of tested patients, about 75%, reported that the test helped decision making, yet a small percentage [25%] did not recall their test status."**
>
> —STEVEN J. KATZ, MD, MPH

Sixty-nine percent of the 3781 women with breast cancer—from the Georgia and Los Angeles SEER registries—who were approached by Katz and his team, responded to the survey. Katz said that while the average age of the women who participated was older, they had a wide distribution of age, ethnicity, and income. The women, who had received treatment in 2013 and 2014, were asked to answer questions related to their oncologist's treatment recommendations, chemotherapy receipt, and treatment decision satisfaction. More than 1200 patients with stage I/II, ER+, HER2- disease were categorized into 3 groups:

1. Node-negative favorable (no high-risk features)
2. Node-negative, less favorable (age at diagnosis less than 50 years or grade 3 tumor)
3. Node-positive.

The regression analysis conducted on this data was adjusted for comorbidity, education, income, race, location, and sampling design.[1]

Katz showed that in the sample of women who were evaluated, recommendations for chemotherapy and receipt of chemotherapy were both in line with their respective risk scores: a majority of those tested received a recommendation for, and subsequent chemotherapy treatment (see **TABLE** below). "While a majority of tested patients, about 75%, reported that the test helped decision making, yet a small percentage [25%] did not recall their test status," Katz said.

Katz believes that the RS assay is genuinely concordant with node-negative disease, and test uptake is substantial even in patients with node-positive disease. "Patients seem to shift toward less chemotherapy, rather than altered treatment, following RS score," he said, adding that the effect was most evident in women with less favorable prognosis.

"The TAILORx[2] and RxPONDER[3] trials will refine the treatment algorithms further, following the test for recurrence score," Katz said.

The Trial Assigning IndividuaLized Options for Treatment (Rx) (TAILORx) and Rx for Positive NoDe Endocrine Responsive Breast Cancer (RxPONDER) trials are examining wheth-

TABLE. Recurrence Score and Subsequent Treatment in Stage I/II Breast Cancer Patients

	Node-negative, favorable (n = 718)		Node-negative, unfavorable (n = 283)		Node-positive (n = 286)	
	Node-positive (n = 286)	Got chemo	Recommended against/neutral/for	Got chemo	Recommended against/neutral/for	Got chemo
No test (608)	54/21/25	14	25/9/66	59	9/9/82	83
RS						
0-17 (427)	78/10/12	3	64/11/25	6	49/12/39	22
18-30 (204)	38/19/43	38	20/25/55	52	9/22/69	64
>30 (48)	0/0/100	100	3/5/92	94	0/0/200	100

Chemo indicates chemotherapy; RS, recurrence score.

THE AMERICAN JOURNAL OF MANAGED CARE

er genes that are frequently associated with RR for women with early-stage breast cancer can be used to assign patients to the most appropriate and effective treatment. EBO

REFERENCES

1. Katz SJ, Friese CR, Li Y, et al. Clinical use of the 21-gene assay and patient experiences in early-stage breast cancer. *J Clin Oncol.* 2016;34 (suppl; abstract 6501).

2. The TAILORx breast cancer trial. National Cancer Institute website. http://www.cancer.gov/types/breast/research/tailorx. Accessed June 6, 2016.

3. RxPONDER trial: Treatment options. SWOG website. http://swog.org/Visitors/S1007/treatment.asp. Accessed June 6, 2016.

Cancer Drug Prices Follow a Sharp Upward Trajectory Post Launch

SURABHI DANGI-GARIMELLA, PHD

A study presented at the annual meeting of the American Society of Clinical Oncology by a group from Israel that evaluated the price trend of 30 anticancer agents following their launch, found that prices may increase by as much as 44% even after adjusting for inflation.

Noa Gordon, MSc, MPH, Davidoff Centre, Rabin Medical Centre, shared findings from their research that measured the price trajectory of 30 patented infusion cancer drugs (all Medicare Part B drugs), following their launch in the United States. Quarterly changes in prices of average monthly doses for these drugs, approved by the FDA between 1996 and 2012, were documented. The study specifically excluded cytokine therapies, hormonal therapies, autologous immunotherapies, and drugs that lost FDA approval. The group used the average sales price (ASP) to be able to account for discounts and rebates, as published by the CMS. Additionally, prices were adjusted for inflation.

Gordon said that their study found a mean annual ASP change of 3.75% and a mean cumulative ASP change of 28%. The mean cumulative inflation-adjusted ASP change was 15%. These changes were during a follow-up period of 11.5 years.

"Rituximab and trastuzumab follow a similar pattern in price increase over time, and inflation-adjusted prices rose since approval by 44% and 40% respectively," Gordon said. The inflation-adjusted price of pemetrexed rose by 26%. Additionally, clustering drugs for indication, year of approval, and company did not identify any significant trends, Gordon said.

The TABLE lists the changes for 10 of the 30 drugs that were evaluated by Gordon's group.

When they evaluated off-patent drugs, they observed about a 95% to 97% decrease in the price of 7 drugs after they went off patent. Another example that Gordon highlighted was the impact of added indications on drug price—the price of ipilimumab, she showed, has increased by 11% over the last 5 years following its approval.

The major limitations of the study, Gordon said, were that they accounted for only the Medicare Part B rates. Additionally, the ASP prices may change or differ based on consumers.

Gordon concluded, "Cancer drug prices may change substantially following launch, and prices may increase by as much as 44%, even after adjusting for inflation. So, when discussing value, we must take into account that prices are not always static," she said. EBO

REFERENCE

Gordon N, Stemmer SM, Greenberg D, Goldstein DA. Price trajectory of individual cancer drugs following launch. *J Clin Oncol.* 2016;34 (suppl; abstract 6502).

The study found a mean annual average sales price (ASP) change of 3.75% and a mean cumulative ASP change of 28%. The mean cumulative inflation-adjusted ASP change was 15%.

"Cancer drug prices may change substantially following launch, and prices may increase by as much as 44%, even after adjusting for inflation. So, when discussing value, we must take into account that prices are not always static."

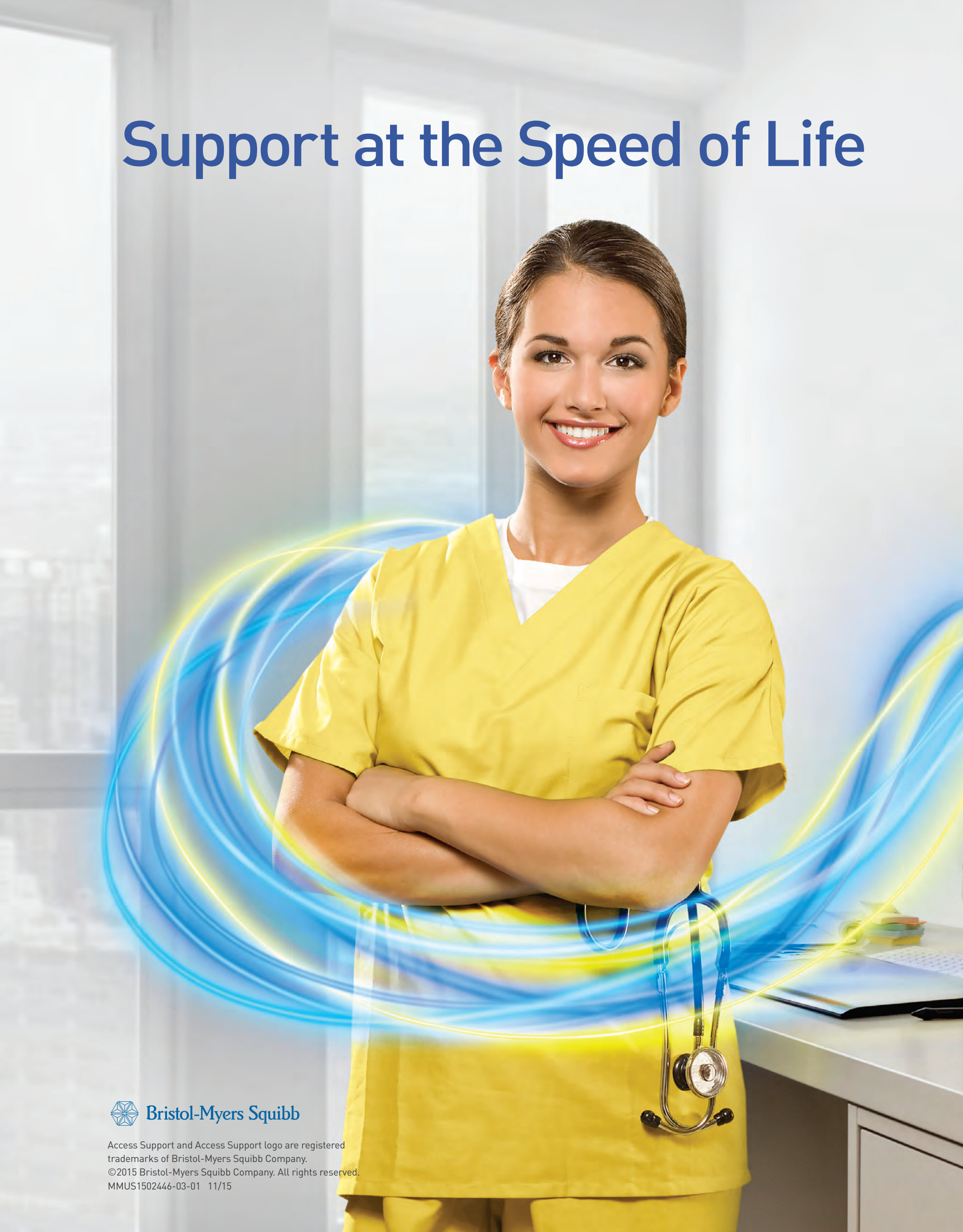
—NOA GORDON, MSC, MPH

TABLE. Changes in Annual ASP of 10 Commonly Used Anticancer Agents

Generic name	Follow-up time (years)	ASP change (US$)	ASP change (%)	Inflation-adjusted ASP change (%)
rituximab	11	3041	74	44
trastuzumab	11	2396	69	40
pemetrexed	11	2632	52	26
panitumumab	8	2020	25	12
bevacizumab	11	2258	24	3
nab-paclitaxel	10	1578	20	2
ipilimumab	4	4660	11	8
cetuximab	11	78	8	-10
denosumab	4	127	7	4
pertuzumab	2	143	3	3

ASP indicates average sales price.

Support at the Speed of Life



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Understanding and Mitigating the Financial Burden of Cancer Patients

SURABHI DANGI-GARIMELLA, PHD


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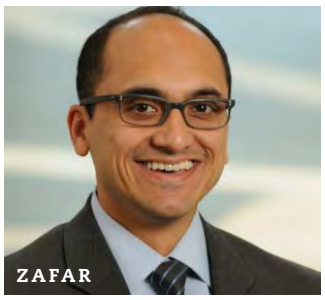

ZAFAR

> **“Financial toxicity is a constellation of symptoms. Patients face difficulty meeting household expenses, they face financial stress/strain, loss of employment and income, debt, and bankruptcy.”**
>
> —VEENA SHANKARAN, MD, MS

Healthcare is expensive, and patients, as well as physicians are increasingly aware of the unsustainable nature of the rising cost. Drug prices are a significant piece of this equation, and have developed into the fastest growing segment of healthcare costs—however, the cost of healthcare services is also a burden on the patient’s wallet. So what can providers do? What can patients do? An Education Session on the second day of the annual meeting of the American Society of Clinical Oncology, held in Chicago, June 3-7, 2016, delved into these problems, queried their impact on patient behavior and clinical outcomes, and suggested potential solutions.

The session was chaired by Veena Shankaran, MD, MS, a health policy researcher at the University of Washington. She was joined by Dawn L. Hershman, MD, MS, who heads the Breast Cancer Program at Columbia University Medical Center, and Yousuf Zafar, MD, MHS, a health policy researcher at Duke University Medical Center.

Shankaran, who authored an article on financial toxicity in *Evidence-Based Oncology* last year,[1] spoke about Risk Factors and Clinical Implications of Financial Toxicity.

“Cancer drug spend, as well as cancer care spending surpasses overall healthcare spending, and simultaneously, annual insurance costs are rising at a steady pace,” Shankaran said. She shared data that showed the combination of premiums and out-of-pocket (OOP) costs rose from about $3000 per year in 2008, to more than $5000 per year in 2015. Patients are facing higher copays and coinsurance, while access to treatment has barriers, defined by restrictive prescription plans and 4-tier drug formularies. “This is particularly important in oncology where there’s been a sharp rise in the approval of oral anticancer agents,” she said. Shankaran shared data plots that showed the total annual spending per user is significantly higher in cancer ($80,466) over treatments outside cancer ($21,048), and the annual beneficiary cost share for patients with cancer is on average $6000 greater.

When comparing the OOP spending for cancer patients, a study by the LIVESTRONG foundation found that across a variety of insurance plans, a greater percentage of cancer patients spent more on their medical expenses compared with patients with other chronic conditions.[2]

“Financial toxicity is a constellation of symptoms. Patients face difficulty meeting household expenses, they face financial stress/strain, loss of employment and income, debt, and bankruptcy,” Shankaran said. This can also take a psychological toll on the patient and impact their quality of life, she said.

It’s important to consider what factors predispose cancer patients to financial hardships. Research by Shankaran’s own group at Fred Hutch has identified several such risk factors[3]:

- Younger age
- Lower income
- Non-white
- Advanced and/or aggressive cancers
- Comorbidities
- Lack of supplemental insurance

She stressed that younger age seems to be the most significant risk factor, and what this could ultimately lead to is an impact on clinical outcomes, resulting from issues with adherence, access, and trial participation, finally resulting in reduced survival. According to Shankaran, the problem requires a multifaceted solution, and lowering drug prices alone cannot mend the damage. A combination of short- and long-term interventions with contributions from policy makers, patients, providers, and payers are necessary. These would include addressing:

- Sustainable drug pricing
- Cost transparency
- Communication on costs
- Financial counseling and/or navigation
- Medical debt reform
- Changes within the Affordable Care Act

Hershman, who heads the Breast Cancer Program at Columbia University Medical Center, addressed adherence issues that crop up as patients try to cope with their copays and OOP costs, particularly the high OOP of oral medications.

“Adherence is a global issue, and in developed countries, studies have shown that adherence in chronic conditions is only about 50%,” Hershman said. However, adherence is a difficult outcome to measure, and patients are our best source of information, she said, emphasizing that patient-provided “information cannot be very reliable. We can also use [electronic health records] or microelectronic monitoring systems to follow patient adherence to the regimen.”

Hershman suggested several points of intervention, including toxicity, cost, and behavior, adding “cost is the most modifiable risk.”

Does cost impact adherence? Research by Hershman’s group found an association between copayment and nonpersistence—an inverse correlation between the 2 variables. Specifically, in a cohort of patients older than 65 years, if the monthly OOP spending on a 90-day supply of their medication exceeded $30 per month, significant nonadherence was observed.[4]

Patients on a once-a-month prescription showed a similar trend: those who spent less than $10 per month had better adherence than those who spent greater than $20 per month. Additional determinants of adherence were generic versus brand-name drugs and household income.

“We need to strike a balance between cost of drugs and innovation,” Hershman said. One immediate solution is the Cancer Drug Coverage Parity Act (2007), which states that patients should not pay more for oral drugs over intravenous infusions. “While a few states have adopted this act, others are thinking about it as well, and there could be a change seen soon,” Hershman told the audience.

Zafar, who has coined the term “financial toxicity,” made the final presentation. He believes that innovative benefit designs and changes in the reimbursement structure can help address the problem at hand.

“Toxicity can impact patient well-being, quality of life, and the quality of care. All together it can worsen patient outcomes.” So while we think about clinical toxicity, we also need to think of reducing the burden of financial toxicity, Zafar said. “We should think of financial toxicity as a symptom. Treating the symptom at an individual patient level is much more manageable to handle than a systemwide change in policies.”

Zafar’s suggestions for reducing the financial burden on patients include:

- Think about the value of what we prescribe. Avoid low-value interventions (follow ABIM's Choosing Wisely recommendations).
- Think about shared goals-of-care discussions

Zafar told the audience about "Finance," a financial assistance, navigation, communication, and education tool that his group is in the process of fine-tuning. "It provides patients with insurance information, helps them understand their coverage policy, helps guide their discussions with oncologists, and helps them navigate sources of financial help," he said.

Zafar also stressed the importance of following a patient's financial distress over time. While 52% of patients want to talk to their oncologists about their financial problems, only 19% attempted a discussion.[5] "When we asked those 19% if the discussions with their oncologist had an impact on their OOP costs, 57% said 'Yes.' How did this happen?" Zafar explained that several factors were identified as a significant influence on OOP costs, including the physician making a case with the insurance company, as well as the patients making a more informed decision on their health coverage. **EBO**

REFERENCES

1. Shankaran V. The financial impact of cancer care: implications and potential solutions. *Am J Manag Care*. 2015; 21(SP16): SP547-SP550).
2. Banegas MP, Guy Jr GP, de Moor JS, et al. For working-age cancer survivors, medical debt and bankruptcy create financial hardships. *Health Aff*. 2016. 35(1):54-61. doi: 10.1377/hlthaff.2015.0830.
3. Shankaran V, Jolly S, Blough D, Ramsey SD. Risk factors for financial hardship in patients receiving adjuvant chemotherapy for colon cancer: a population-based exploratory analysis. *J Clin Oncol*. 2012;30(14):1608-1614. doi: 10.1200/JCO.2011.37.9511.
4. Neugut AI, Subar M, Wilde ET, et al. Association between prescription co-payment amount and compliance with adjuvant hormonal therapy in women with early-stage breast cancer. *J Clin Oncol*. 2011; 29(18): 2534-2542. doi: 10.1200/JCO.2010.33.3179.
5. Zafar SY, Chino F, Ubel PA, et al. The utility of cost discussions between patients with cancer and oncologists. *Am J Manag Care*. 2015;21(9):607-615.

ASCO Study Finds Daratumumab Could Be Economical Over Pomalidomide-Dexamethasone in MM

SURABHI DANGI-GARIMELLA, PHD

Daratumumab was FDA approved[1] late last year for the treatment of patients with multiple myeloma (MM) who had received at least 3 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are double refractory (DR) to a PI and an IMiD. A poster presented at the annual meeting of the American Society of Clinical Oncology evaluated the cost per median month of survival (mOS) for daratumumab and other novel MM treatments.

A team of health economists at Janssen Pharmaceuticals developed a model to estimate the average cost per mOS in patients with MM who either received at least 3 prior lines of treatment or were DR to a PI and an IMiD; received at least 3 prior lines of treatment regardless of DR status; or were DR to a PI and an IMiD regardless of number of prior lines of treatment. Daratumumab, carfilzomib, and pomalidomide+dexamethasone (POM+D) were included in the analysis.[2] The time of the study was the duration of overall survival of each therapy.

The drug costs were based on Wholesale Acquisition Costs (WACs), and discounting was not applied for the study. The costs included in the analysis were:

- Drug
- Pre- and postmedication
- Administration
- Monitoring
- Auxiliary
- Adverse events (AEs)

Monitoring, auxiliary, and AE costs were based on Medicare fee schedules and publications. Treatment duration was assumed to be median progression-free survival. The cost per month of mOS was the sum of drug costs, pre- and postmedication costs, administration costs, monitory and auxiliary costs, and AE costs, divided by the mOS in months.

The study found that the mOS for the 3 treatment groups was:

- $4264 for daratumumab
- $4884 (FOCUS trial) and $4213 (PZ-171-003-A1 trial) for carfilzomib
- $5536 for POM+D

The maximum contribution to the monthly cost was the price of the drug, followed by costs to treat AEs or administration costs. Carfilzomib had the lowest drug cost, the study found. Daratumumab had the lowest monitoring and auxiliary costs per month of mOS, and it was also associated with the lowest AEs costs per month. Pomalidomide had the highest monthly costs associated with AEs.

While a significant drawback of the study is the use of WACs, because they are not an accurate reflection of a drug cost and might actually be an overestimation of the actual cost to payers, this study can be the foundation for designing future economic analyses of treatments for MM. **EBO**

The maximum contribution to the monthly cost was the price of the drug, followed by costs to treat adverse events or administration costs.

REFERENCES

1. Dangi-Garimella S. Daratumumab approval yields the first monoclonal antibody, and another option, in multiple myeloma. *The American Journal of Managed Care* website. http://www.ajmc.com/newsroom/daratumumab-approval-yields-the-first-monoclonal-antibody-and-another-option-in-multiple-myeloma. Published November 16, 2015. Accessed June 22, 2016.
2. Maiese EM, Dimova M, Baio G, Makin C. Cost per median overall month of survival in multiple myeloma patients with ≥3 lines of therapy or were double refractory. *J Clin Oncol*. 2016;34 (suppl; abstract 8057).

AJMCtv Interviews

Experts discuss new value tools, payment and care delivery models, and the financial burden faced by patients with cancer.

PRODUCED BY NICOLE BEAGIN

Dr John Fox Expects the Oncology Medical Home Model to Decrease Costs

The key to driving down costs or, at the very least, making costs more predictable, is integrating pathways into the Oncology Care Model program, said John L. Fox, MD, MS, associate vice president of medical affairs at Priority Health.

CAN WE DRAW PARALLELS BETWEEN PAYER-DRIVEN CLINICAL PATHWAYS AND THE ONCOLOGY MEDICAL HOME MODEL?

Medicare's Oncology Care Model, which I'm not an expert on, I think has a potential to drive down the cost of healthcare without impacting patient outcomes. There are a number of ways that can happen. One is that the cost of care will become more predictable because the regimens that providers use will have a more predictable cost.

In our experience with our Oncology Medical Home initiative, where we ask providers to develop pathways around high-volume conditions—and not only pathways, but preferred regimens—we very clearly showed that providers tended to choose the less costly regimens. So, I think that integration of pathways into an Oncology Care Model program is not only essential, but that's what will help drive down costs, at least make costs more predictable.

But more importantly, I think the pathways have to include or embed advanced care planning. The trends for increasing costs of drugs don't suggest that will drive down the costs of care simply by having pathways. But if those pathways include discussions of patient preferences and goals of care, then I think it increases the likelihood that will diminish the amount of chemotherapy we'll give to patients at the end-of-life, because they'll have said, "My goals can be obtained in ways other than chemotherapy."

Dr Bhuvana Sagar on Using Data Generated From Value Frameworks

Although Cigna's reimbursement medical home model is still in its very early stages, Bhuvana Sagar, MD, national medical director of Cigna Healthcare, explained that discussing value in healthcare and getting back to smarter spending, as well as better outcomes for patients, should be the focus of all industry stakeholders.

WILL THE INFORMATION GENERATED FROM THE VARIOUS VALUE FRAMEWORKS OUT THERE INFLUENCE REIMBURSEMENT DECISIONS BY CIGNA?

Definitely, definitely. So, what we're trying to do is we're trying to get as much data as possible, and at this point, with our reimbursement medical home models that we have in place—these have been there only for a short time, relatively a short time, probably about a year—we're still trying to get data, we're still trying to get experience with the program, providers are still getting used to it, customers are still trying to get used to it.

So, once we have more information, we're definitely going to look and see what works, what doesn't work, and where the greatest impact is going to be, and go from there. Why do you think we need to have the value discussion in healthcare today? Well, with rising healthcare costs, we can't continue to ignore them at this point, and we, as a society, need to do something to address the cost. You know, the different stakeholders need to be involved in the discussion, and we've come to a point where we all understand that the fee-for-service system just seems to be adding a lot of that volume without necessarily affecting the quality of care.

So we want to go back to what's important. We want to have smarter spending, better outcomes for our patients, and overall better healthcare for our patients.

Dr Michael Kolodziej Says Insurers May Never Use Value Frameworks

With value frameworks still in their infancy, Michael Kolodziej, MD, national medical director for oncology strategy at Aetna, doesn't see how his company can use them just yet. In fact, these frameworks may never be used by insurers; they may only be used for shared decision making between the patient and provider.

DOES AETNA PLAN TO LEVERAGE THE VALUE CALCULATORS AND FRAMEWORKS THAT ARE NOW AVAILABLE?

At the present time, no. And I think part of that is because they are all works in progress. Now, I will say, and I have said this multiple times, I applaud everybody who is working in this space around their courage, in attempting to objectively define a way of measuring value; having worked in the clinical pathways space for a long time, that was basically the same thing. The better thing now is that people seem to have caught the virus of being interested in quantifying value, but there are some important things missing that make it really, really hard for me to totally embrace them.

The 2 most important things that are missing are the element of real-world evidence—and I think we need to support efforts to collect real-world evidence—and, second of all, the patient voice is not adequately represented. I think those are solvable problems, and as we look to the next set of iterations, we will see attempts to incorporate them. But speaking from the insurance company point-of-view, I don't see a way that the insurance company is going to use them. But I do see a way that they are going to become an important component of shared decision making at the physician–patient level.

MD MAGAZINE
The CMS transition to paying for value-based care at **http://bit.ly/29bI41Q**.

To listen to the experts, please visit
http://www.ajmc.com/conferences/asco2016.

Dr Stephen Grubbs Explains How ASCO Is Modifying Its Value Framework

More than 400 comments were sent in regarding the American Society of Clinical Oncology (ASCO)'s Value Framework, and they will be incorporated as the framework evolves, explained Stephen Grubbs, MD, vice president for clinical affairs at ASCO.

ARE THERE PLANS TO USE FEEDBACK FROM THE FIELD TO MODIFY THE ASCO VALUE FRAMEWORK?

So, the publication was done last year with the idea that people would comment upon that, and there's been over 400 comments sent in to ASCO on this, and they are being taken into consideration, and there are modifications of the tool. And beyond the comments, the tool needs to get more sophisticated in what it's measuring. I'll give you an example.

Right now, we're measuring the net health benefit based on the advantage you get from the treatment, but also the toxicities of the drugs. But we need to expand the negative part of that into, "How does it affect your family? How does it affect your quality of life? Can we get patient-reported outcomes involved in all this?" So this is going to become very, very sophisticated, but at least the skeleton is there to build on right now.

This is not ready for prime time, but the conversation is going on, the modifications are being made, and we hope to see this evolve into an actually usable instrument where you might have a software program in your office where you can sit there with that patient. Of course, when you get to the cost part of it, that's different for every patient. It's what payers are willing to pay for, and then, what is their responsibility part of that. So you have to adjust that per patient.

Dr Lucio Gordan Names His Most Exciting Development in Oncology in the Last Year

New immunotherapies and biologics that are changing the landscape when it comes to treating patients are the most exciting development in oncology in the last year, according to Lucio Gordan, MD, of Florida Cancer Specialists.

THERE HAVE BEEN A NUMBER OF DEVELOPMENTS IN ONCOLOGY TREATMENT IN THE LAST YEAR. WHICH OF THOSE DO YOU FIND THE MOST CLINICALLY EXCITING?

There are several. Obviously, we cannot go into oncology without speaking about immunotherapy, the new biologics. Those drugs are potentially changing the landscape as to how we treat patients with lung cancer, melanoma, and others. So, I think this is the most critical component as far as developments. We have had several new drugs approved for multiple myeloma for this year and how to sequence these drugs is a challenge.

Another important point of the clinical track that we discuss for the community of oncology physicians is to make sure that we always support clinical trial enrollment. This is the only way we can move the science forward and get our patients to do better. But, I think immunotherapy is the blockbuster for 2016.

Dr Debra Patt Acknowledges Progress Made Against Cancer

One of the important findings from the American Society of Clinical Oncology (ASCO)'s report is that cancer mortality has gone down, said Debra Patt, MD, MPH, MBA, director of public policy at Texas Oncology.

WHAT WERE SOME OF THE KEY FINDINGS FROM ASCO'S ANNUAL REPORT ON THE STATE OF CANCER CARE IN THE UNITED STATES?

Well, I think one of the most important things that we recognize today is that while we're seeing more cancer, cancer mortality continues to go down. So, one of the findings in the report was that cancer mortality, in fact, has gone down by 1.5% per year for the last decade. I think that's representative of progress: progress in screening and early detection, progress in more effective immediate therapies, progress in long-term therapies, and even in patients with incurable illness, that they live longer. Those are great successes.

Patricia Goldsmith Describes the Financial Challenges Oncology Patients Face

CancerCare provides oncology patients with many services that offer both educational and financial support, as well as any help the patient may need with his or her family, such as child care and housekeeping needs. However, Patricia Goldsmith, CEO of CancerCare, explained that there are many financial challenges, including transportation and high out-of-pocket costs, that oncology patients continue to face.

HOW DOES CANCERCARE ASSIST ONCOLOGY PATIENTS?

CancerCare assists oncology patients in many different ways. Last year, we directly served 180,000 individuals in 90% of the counties in the United States. We did that through the work of 42 masters-prepared oncology social workers that actually provide free counseling, free group counseling, free support services. In addition, we also provide education where we use [key opinion leaders] who actually present 1-hour workshops on many different topics in cancer.

Last year, we conducted 58 of those that reached 70,000 individuals. In addition, we are the largest provider of non–co-pay financial support to help individuals with their transportation, child care needs, housekeeping services, and meals, and we gave out approximately $5 million for that last year. We also provide co-payment assistance through a co-payment foundation, free wigs, [and] breast prosthesis, as well as bereavement camp and many other services.

WHAT ARE THE BIGGEST CHALLENGES WITH TREATMENT THAT PATIENTS APPROACH CANCERCARE WITH?

Sixty percent of the individuals that approach CancerCare are actually looking for some form of financial assistance. But, what we do find is that it's not just financial support that those individuals need. The largest request for financial support actually comes for transportation. Money that individuals need to either go to a clinical trial, participate in a trial, or actually to be able to afford gasoline or cab fare to their physician's appointments.

So, financial issues are very large. But the distress and the psychosocial issues are also very large for individuals and for their families. Cancer is not just a disease of the patient. It impacts the entire family, so there are many different services that individuals need.

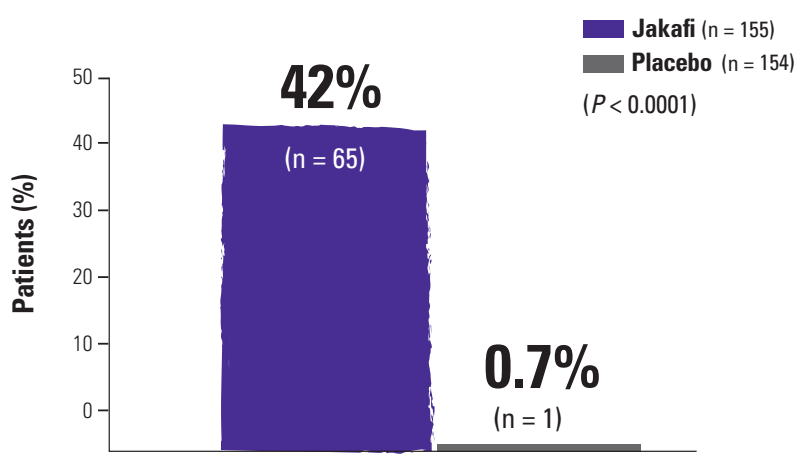
Provide your members with the option that's

FDA APPROVED FOR INTERMEDIATE OR HIGH-RISK MYELOFIBROSIS

Significantly more patients with intermediate-2–risk or high-risk myelofibrosis receiving Jakafi® (ruxolitinib) achieved the primary end point compared with placebo (COMFORT-I*) or best available therapy† (COMFORT-II‡)[1-3]

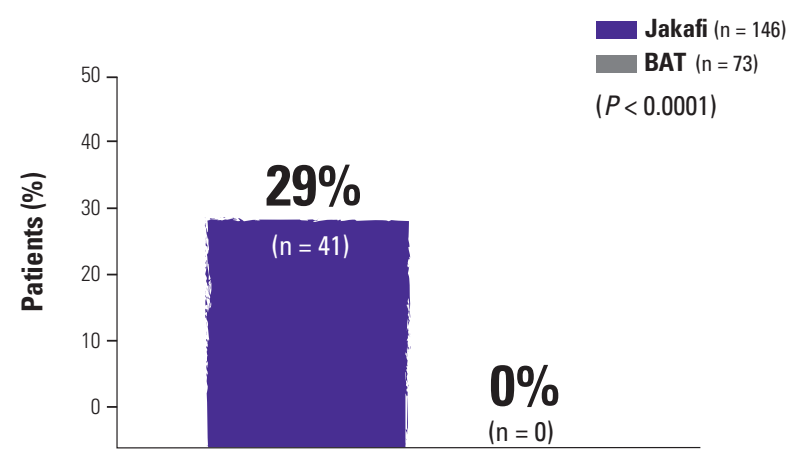
- The primary end point was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline at week 24 as measured by CT or MRI[1,2]

COMFORT-I Primary End Point: Spleen Volume Reduction at Week 24[1,2]



- The primary end point was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline at week 48 as measured by CT or MRI[1,3]

COMFORT-II Primary End Point: Spleen Volume Reduction at Week 48[1,3]



BAT, best available therapy.

* COMFORT-I (COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment-I) was a randomized, double-blind, placebo-controlled phase 3 study with 309 patients with intermediate-2–risk and high-risk myelofibrosis.[1,2]

† Best available therapy in COMFORT-II included hydroxyurea (46.6%) and glucocorticoids (16.4%), as well as no medication, anagrelide, epoetin alfa, thalidomide, lenalidomide, mercaptopurine, thioguanine, danazol, peginterferon alfa-2a, interferon-α, melphalan, acetylsalicylic acid, cytarabine, and colchicine.[4]

‡ COMFORT-II (COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment-II) was a randomized, open-label phase 3 study with 219 patients with intermediate-2–risk and high-risk myelofibrosis.[1,3]

Important Safety Information

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC $<0.5 \times 10^9$/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines

Incyte

Jakafi® ruxolitinib (tablets)

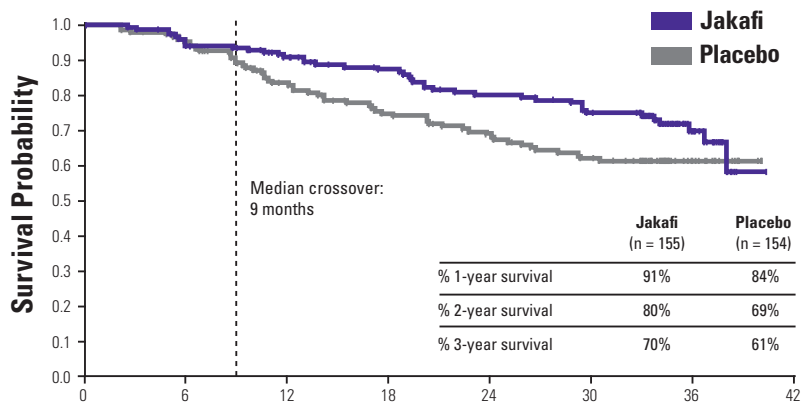
Indications and Usage

Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post–polycythemia vera myelofibrosis and post–essential thrombocythemia myelofibrosis.

Overall survival was a prespecified secondary end point in COMFORT-I and COMFORT-II[1]

- COMFORT-I: At 3 years, survival probability was 70% for patients originally randomized to Jakafi and 61% for those originally randomized to placebo[1]
- COMFORT-II: At 3 years, survival probability was 79% for patients originally randomized to Jakafi and 59% for those originally randomized to best available therapy[1]

COMFORT-I Overall Survival: Kaplan-Meier Curves by Treatment Group[1]

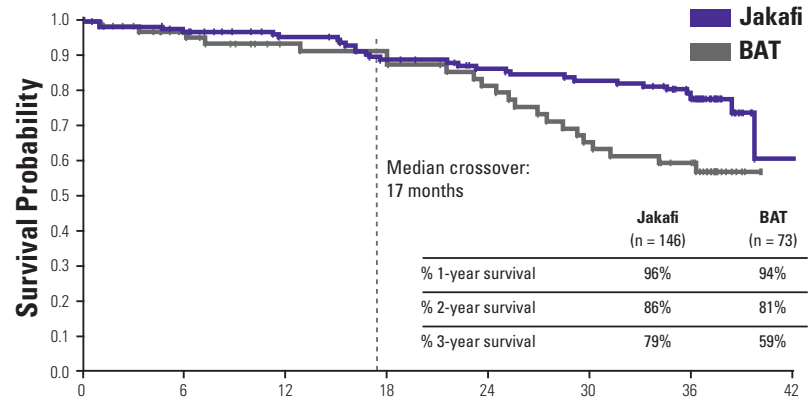


	Jakafi (n = 155)	Placebo (n = 154)
% 1-year survival	91%	84%
% 2-year survival	80%	69%
% 3-year survival	70%	61%

Number of patients at risk

Jakafi	155	145	134	122	111	102	29	0
Placebo	154	142	117	101	92	82	32	0

COMFORT-II Overall Survival: Kaplan-Meier Curves by Treatment Group[1]



	Jakafi (n = 146)	BAT (n = 73)
% 1-year survival	96%	94%
% 2-year survival	86%	81%
% 3-year survival	79%	59%

Number of patients at risk

Jakafi	146	135	126	115	107	104	33	0
BAT	73	58	50	47	42	33	9	0

BAT, best available therapy.

- Because of progression-driven events or at the physician's discretion, patients randomized to placebo (COMFORT-I) or best available therapy (COMFORT-II) who crossed over to receive Jakafi continued to be grouped within their original randomized assignment for analysis purposes[4]

- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation
- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- The three most frequent non-hematologic adverse reactions (incidence >10%) were bruising, dizziness and headache
- A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breast-feed

Please see Brief Summary of Full Prescribing Information for Jakafi on the following pages.

To learn more about Jakafi, visit **Jakafi.com/HCP**.

References: 1. Jakafi Prescribing Information. Wilmington, DE: Incyte Corporation. **2.** Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med.* 2012;366(9):799-807. **3.** Harrison C, Kiladjian J-J, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med.* 2012;366(9):787-798. **4.** Data on file. Incyte Corporation. Wilmington, DE.

Jakafi®
ruxolitinib (tablets)

BRIEF SUMMARY: For Full Prescribing Information, see package insert.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [*see Dosage and Administration (2.1) in Full Prescribing Information*]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [*see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 X 10^9/L) was generally reversible by withholding Jakafi until recovery [*see Adverse Reactions (6.1) in Full Prescribing Information*]. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. [*see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*].

Risk of Infection Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. *Tuberculosis* Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. *PML* Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate. *Herpes Zoster* Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [*see Adverse Reactions (6.1) in Full Prescribing Information*]. *Hepatitis B* Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. **Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi** Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with myelofibrosis have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [*see Dosage and Administration (2.5) in Full Prescribing Information*], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. **Non-Melanoma Skin Cancer** Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. **Lipid Elevations** Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

ADVERSE REACTIONS The following serious adverse reactions are discussed in greater detail in other sections of the labeling: • Thrombocytopenia, Anemia and Neutropenia [*see Warnings and Precautions (5.1) in Full Prescribing Information*] • Risk of Infection [*see Warnings and Precautions (5.2) in Full Prescribing Information*] • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [*see Warnings and Precautions (5.3) in Full Prescribing Information*] • Non-Melanoma Skin Cancer [*see Warnings and Precautions (5.4) in Full Prescribing Information*]. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. **Clinical Trials Experience in Myelofibrosis** The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with myelofibrosis in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 X 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 X 10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse drug reactions were thrombocytopenia and anemia [*see Table 2*]. Thrombocytopenia, anemia and neutropenia are dose related effects. The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache [*see Table 1*]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 1: Myelofibrosis: Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

	Jakafi (N=155)			Placebo (N=151)		
Adverse Reactions	**All Grades[a] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Bruising[b]	23	<1	0	15	0	0
Dizziness[c]	18	<1	0	7	0	0
Headache	15	0	0	5	0	0
Urinary Tract Infections[d]	9	0	0	5	<1	<1
Weight Gain[e]	7	<1	0	1	<1	0
Flatulence	5	0	0	<1	0	0
Herpes Zoster[f]	2	0	0	<1	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes contusion, ecchymosis, hematoma, injection site hematoma, periorbital hematoma, vessel puncture site hematoma, increased tendency to bruise, petechiae, purpura
[c] includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthitis
[d] includes urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, nitrite urine present
[e] includes weight increased, abnormal weight gain
[f] includes herpes zoster and post-herpetic neuralgia

Description of Selected Adverse Drug Reactions **Anemia** In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (<1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients. **Thrombocytopenia** In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50 X 10^9/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in <1% of patients receiving Jakafi and <1% of patients receiving control regimens. Patients with a platelet count of 100 X 10^9/L to 200 X 10^9/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 X 10^9/L (17% versus 7%). **Neutropenia** In the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study[a]

	Jakafi (N=155)			Placebo (N=151)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Thrombocytopenia	70	9	4	31	1	0
Anemia	96	34	11	87	16	3
Neutropenia	19	5	2	4	<1	1

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Additional Data from the Placebo-controlled Study 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was <1% for Jakafi with no Grade 3 or 4 AST elevations. 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations. **Clinical Trial Experience in Polycythemia Vera** In a randomized, open-label, active-controlled study, 110 patients with polycythemia vera resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy [*see Clinical Studies (14.2) in Full Prescribing Information*]. The most frequent adverse drug reaction was anemia. Table 3 presents the most frequent non-hematologic treatment emergent adverse events occurring up to Week 32. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi.

Table 3: Polycythemia Vera: Treatment Emergent Adverse Events Occurring in ≥ 6% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

	Jakafi (N=110)		Best Available Therapy (N=111)	
Adverse Events	**All Grades[a] (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Headache	16	<1	19	<1
Abdominal Pain[b]	15	<1	15	<1
Diarrhea	15	0	7	<1
Dizziness[c]	15	0	13	0
Fatigue	15	0	15	3
Pruritus	14	<1	23	4
Dyspnea[d]	13	3	4	0
Muscle Spasms	12	<1	5	0
Nasopharyngitis	9	0	8	0
Constipation	8	0	3	0
Cough	8	0	5	0
Edema[e]	8	0	7	0
Arthralgia	7	0	6	<1
Asthenia	7	0	11	2
Epistaxis	6	0	3	0
Herpes Zoster[f]	6	<1	0	0
Nausea	6	0	4	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes abdominal pain, abdominal pain lower, and abdominal pain upper
[c] includes dizziness and vertigo
[d] includes dyspnea and dyspnea exertional
[e] includes edema and peripheral edema
[f] includes herpes zoster and post-herpetic neuralgia

Other clinically important treatment emergent adverse events observed in less than 6% of patients treated with Jakafi were: Weight gain, hypertension, and urinary tract infections. Clinically relevant laboratory abnormalities are shown in Table 4.

Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment[a]

	Jakafi (N=110)			Best Available Therapy (N=111)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Hematology						
Anemia	72	<1	<1	58	0	0
Thrombocytopenia	27	5	<1	24	3	<1
Neutropenia	3	0	<1	10	<1	0
Chemistry						
Hypercholesterolemia	35	0	0	8	0	0
Elevated ALT	25	<1	0	16	0	0
Elevated AST	23	0	0	23	<1	0
Hypertriglyceridemia	15	0	0	13	0	0

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

DRUG INTERACTIONS Drugs That Inhibit or Induce Cytochrome P450 Enzymes Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9. **CYP3A4 inhibitors:** The C_{max} and AUC of ruxolitinib increased 33% and 91%, respectively following concomitant administration with the strong CYP3A4 inhibitor ketoconazole in healthy subjects. Concomitant administration with mild or moderate CYP3A4 inhibitors did not result in an exposure change requiring intervention [*see Pharmacokinetics (12.3) in Full Prescribing Information*]. When administering Jakafi with strong CYP3A4 inhibitors, consider dose reduction [*see Dosage and Administration (2.3) in Full Prescribing Information*]. **Fluconazole:** The AUC of ruxolitinib is predicted to increase by approximately 100% to 300% following concomitant administration with the combined CYP3A4 and CYP2C9 inhibitor fluconazole at doses of 100 mg to 400 mg once daily, respectively [*see Pharmacokinetics (12.3) in Full Prescribing Information*]. Avoid the concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily [*see Dosage and Administration (2.3) in Full Prescribing Information*]. **CYP3A4 inducers:** The C_{max} and AUC of ruxolitinib decreased 32% and 61%, respectively, following concomitant administration with the strong CYP3A4 inducer rifampin in healthy subjects. No dose adjustment is recommended; however, monitor patients frequently and adjust the Jakafi dose based on safety and efficacy [*see Pharmacokinetics (12.3) in Full Prescribing Information*].

USE IN SPECIFIC POPULATIONS Pregnancy Pregnancy Category C: *Risk Summary* There are no adequate and well-controlled studies of Jakafi in pregnant women. In embryofetal toxicity studies, treatment with ruxolitinib resulted in an increase in late resorptions and reduced fetal weights at maternally toxic doses. Jakafi should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Animal Data* Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There was no evidence of teratogenicity. However, decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). **Nursing Mothers** It is not known whether ruxolitinib is excreted in human milk. Ruxolitinib and/or its metabolites were excreted in the milk of lactating rats with a concentration that was 13-fold the maternal plasma. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Jakafi, a decision should be made 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 Jakafi in pediatric patients have not been established. **Geriatric Use** Of the total number of patients with myelofibrosis in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. **Renal Impairment** The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects [CrCl 72-164 mL/min (N=8)] and in subjects with mild [CrCl 53-83 mL/min (N=8)], moderate [CrCl 38-57 mL/min (N=8)], or severe renal impairment [CrCl 15-51 mL/min (N=8)]. Eight (8) additional subjects with end stage renal disease requiring hemodialysis were also enrolled. The pharmacokinetics of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function. However, plasma AUC values of ruxolitinib metabolites increased with increasing severity of renal impairment. This was most marked in the subjects with end stage renal disease requiring hemodialysis. The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in metabolite exposure. Ruxolitinib is not removed by dialysis; however, the removal of some active metabolites by dialysis cannot be ruled out. When administering Jakafi to patients with myelofibrosis and moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min) with a platelet count between 50 X 10^9/L and 150 X 10^9/L, a dose reduction is recommended. A dose reduction is also recommended for patients with polycythemia vera and moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min). In all patients with end stage renal disease on dialysis, a dose reduction is recommended [*see Dosage and Administration (2.4) in Full Prescribing Information*]. **Hepatic Impairment** The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects (N=8) and in subjects with mild [Child-Pugh A (N=8)], moderate [Child-Pugh B (N=8)], or severe hepatic impairment [Child-Pugh C (N=8)]. The mean AUC for ruxolitinib was increased by 87%, 28% and 65%, respectively, in patients with mild, moderate and severe hepatic impairment compared to patients with normal hepatic function. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1-5.0 hours versus 2.8 hours). The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in ruxolitinib exposure except in the severe (Child-Pugh C) hepatic impairment cohort where the pharmacodynamic activity was more prolonged in some subjects than expected based on plasma concentrations of ruxolitinib. When administering Jakafi to patients with myelofibrosis and any degree of hepatic impairment and with a platelet count between 50 X 10^9/L and 150 X 10^9/L, a dose reduction is recommended. A dose reduction is also recommended for patients with polycythemia vera and hepatic impairment [*see Dosage and Administration (2.4) in Full Prescribing Information*].

OVERDOSAGE There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of ruxolitinib.

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DAY 1

Clinical/Moderator: Joseph Alvarnas, MD

- Immunotherapy update
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- Panel: Immuno-oncology vs precision medicine—Where is cancer care headed?
- Patient education on IO toxicities
- Keynote speaker
- Networking reception
- Patient reception speaker

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DAY 2

Managed Care/Moderators: Bruce A. Feinberg, DO, Joseph Alvarnas, MD

- Value in healthcare
- Panel: How patient-centered are payment models?
- Panel: Managing cancer care costs while ensuring adequate outcomes and quality of care
- New cost sharing models being evaluated by pharmacy benefit managers
- Lack of diagnostic testing coverage: A barrier to patient recruitment
- Does cost sharing influence patient adherence and outcomes in oncology?

Policy/Moderator: Bruce A. Feinberg, DO

- Telehealth in palliative care
- CMS coverage of outpatient palliative care services
- Panel: Oncology care 2017