Bridging the gap between payer and provider perspectives

January 2016
Volume 22
Special Issue 1

THE AMERICAN JOURNAL OF MANAGED CARE®

Evidence-Based Oncology

57TH ANNUAL ASH MEETING 2015 | DECEMBER 5-8 • ORLANDO, FL

AMERICAN SOCIETY OF HEMATOLOGY®

EXCLUSIVE COVERAGE!

HIGHLIGHTS FROM THE MEETING

- Expert FDA reviewers discuss 3 new drugs for multiple myeloma, approved in the same month
- Are patient-reported outcomes an important measure?
- How well does reporting on quality measures tie in with pay-for-performance?
- Latest recommendations by the ASH *Choosing Wisely* Task Force
- Why should hematologists be abreast of alternative payment models?

AJMC® Managed Markets Network®

ANNOUNCING

A Permanent J-code for: OPDIVO® (nivolumab) – J9299

J-code for OPDIVO

HCPCS Code	Description	Effective
J9299[1]	Injection, nivolumab, 1 mg	January 1, 2016

J9299 replaces HCPCS code C9453, injection, nivolumab, 1 mg, and also miscellaneous codes J9999, J3590, and J3490.[1-5]

NDC Codes for OPDIVO[6]

0003-3772-11, 00003-3772-11	40 mg/4 mL (10 mg/mL) solution in a single-use vial
0003-3774-12, 00003-3774-12	100 mg/10 mL (10 mg/mL) solution in a single-use vial

For more information:

- Contact your Area Reimbursement Manager for assistance and to schedule an office visit
- Contact Bristol-Myers Squibb Access Support® at **1-800-861-0048**, Monday-Friday, 8 AM to 8 PM ET
- Visit **www.bmsaccesssupport.com** for resources to help your patients with access to Bristol-Myers Squibb Oncology products

The accurate completion of reimbursement- or coverage-related documentation is the responsibility of the healthcare provider and patient. Bristol-Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item. This coding guidance is not intended to provide specific directions on requesting prior authorization or submitting claims for OPDIVO and does not provide a guarantee of receiving prior authorization or reimbursement. Coding for OPDIVO is dependent on the insurer and the care setting in which the drug will be administered. Oncology practices need to make coding decisions based on the diagnosis and treatment of each patient and the specific insurer requirements.

Indication[6]

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

Select Important Safety Information

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

References

1. Centers for Medicare & Medicaid Services. HCPCS J code. Effective January 1, 2016.
2. 2015 HCPCS Alpha-Numeric Index. Centers for Medicare & Medicaid Services. https://www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/Downloads/2015-Alpha-Numeric-Index-.pdf Accessed November 2, 2015.
3. Centers for Medicare & Medicaid Services. Medicare Claims Processing Manual. Chapter 17 – Drugs and Biologicals. Revision 3292, July 10, 2015. https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/clm104c17.pdf. Accessed October 30, 2015.
4. Medi-Cal. Injections: an overview. https://files.medi-cal.ca.gov/pubsdoco/publications/masters-mtp/part2/injectanover_m00o03o04o11p00.doc. Accessed October 30, 2015.
5. Centers for Medicare & Medicaid Services. HCPCS C-codes. Effective July 1, 2015. http://www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/Downloads/C-Codes-July-2015.zip. Accessed October 30, 2015.
6. OPDIVO (package insert). Princeton, NJ: Bristol-Myers Squibb Company; 2015.

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

IMPORTANT SAFETY INFORMATION

Immune-Mediated Pneumonitis
Immune-mediated pneumonitis or interstitial lung disease, including fatal cases, occurred with OPDIVO® (nivolumab) treatment. Across the clinical trial experience with solid tumors, fatal immune-mediated pneumonitis occurred with OPDIVO. Monitor patients for signs with radiographic imaging and symptoms of pneumonitis. Administer corticosteroids for Grade 2 or greater pneumonitis. Permanently discontinue OPDIVO for Grade 3 or 4 and withhold until resolution for Grade 2. In Checkmate 057, immune-mediated pneumonitis, including interstitial lung disease, occurred in 3.4% (10/287) of patients receiving OPDIVO: Grade 3 (n=5), Grade 2 (n=2), and Grade 1 (n=3).

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

Immune-Mediated Hepatitis
Immune-mediated hepatitis can occur with OPDIVO treatment. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. Withhold OPDIVO for Grade 2 and permanently discontinue for Grade 3 or 4 immune-mediated hepatitis. In Checkmate 057, one patient (0.3%) developed immune-mediated hepatitis.

Immune-Mediated Endocrinopathies
Hypophysitis, adrenal insufficiency, thyroid disorders, and type 1 diabetes mellitus can occur with OPDIVO treatment. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency during and after treatment, thyroid function prior to and periodically during treatment and hyperglycemia. Administer corticosteroids for Grade 2 or greater hypophysitis. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis. Administer corticosteroids for Grade 3 or 4 adrenal insufficiency. Withhold OPDIVO for Grade 2 and permanently discontinue for Grade 3 or 4 adrenal insufficiency. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. Administer insulin for type 1 diabetes. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hyperglycemia. In Checkmate 037, 066, and 057, <1.0% of OPDIVO-treated patients developed adrenal insufficiency. In Checkmate 057, Grade 1 or 2 hypothyroidism, including thyroiditis, occurred in 7% (20/287) and elevated TSH occurred in 17% of patients receiving OPDIVO. Grade 1 or 2 hyperthyroidism occurred in 1.4% (4/287) of patients.

Immune-Mediated Nephritis and Renal Dysfunction
Immune-mediated nephritis can occur with OPDIVO treatment. Monitor patients for elevated serum creatinine prior to and periodically during treatment. For Grade 2 or 3 increased serum creatinine, withhold OPDIVO and administer corticosteroids; if worsening or no improvement occurs, permanently discontinue OPDIVO. Administer corticosteroids for Grade 4 serum creatinine elevation and permanently discontinue OPDIVO. In Checkmate 057, Grade 2 immune-mediated renal dysfunction occurred in 0.3% (1/287) of patients receiving OPDIVO.

Immune-Mediated Rash
Immune-mediated rash can occur with OPDIVO treatment. Severe rash (including rare cases of fatal toxic epidermal necrolysis) occurred in the clinical program of OPDIVO. Monitor patients for rash. Administer corticosteroids for Grade 3 or 4 rash. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4. In Checkmate 057, immune-mediated rash occurred in 6% (17/287) of patients receiving OPDIVO, including four Grade 3 cases.

Immune-Mediated Encephalitis
Immune-mediated encephalitis can occur with OPDIVO treatment. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out other causes. If other etiologies are ruled out, administer corticosteroids and permanently discontinue OPDIVO for immune-mediated encephalitis. Across clinical trials of 8490 patients receiving OPDIVO as a single agent or in combination with ipilimumab, <1.0% of patients were identified as having encephalitis. In Checkmate 057, fatal limbic encephalitis occurred in one patient (0.3%) receiving OPDIVO.

Other Immune-Mediated Adverse Reactions
Based on the severity of the adverse reaction, permanently discontinue or withhold treatment, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. The following clinically significant immune-mediated adverse reactions occurred in <1.0% of OPDIVO-treated patients: uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barre syndrome, hypopituitarism, and systemic inflammatory response syndrome. Across clinical trials of OPDIVO as a single agent administered at doses 3 mg/kg and 10 mg/kg, additional clinically significant, immune-mediated adverse reactions were identified: motor dysfunction, vasculitis, and myasthenic syndrome.

Infusion Reactions
Severe infusion reactions have been reported in <1.0% of patients in clinical trials of OPDIVO as a single agent. Discontinue OPDIVO in patients with Grade 3 or 4 infusion reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. In Checkmate 057 and 066, Grade 2 infusion reactions occurred in 1.0% (5/493) of patients receiving OPDIVO.

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

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

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

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

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

OPDIVO® (nivolumab) injection, for intravenous use

℞ ONLY

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Immune-Mediated Pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of corticosteroids and no clear alternate etiology, including fatal cases, occurred with OPDIVO treatment. Across clinical trial experience with solid tumors receiving OPDIVO as a single agent, fatal immune-mediated pneumonitis occurred in 0.3% (5/1590) of patients. All five fatal cases occurred in a dose-finding study with OPDIVO doses of 1 mg/kg (two patients), 3 mg/kg (two patients), and 10 mg/kg (one patient).

Monitor patients for signs with radiographic imaging and symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or greater pneumonitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold OPDIVO until resolution for moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.4) in full Prescribing Information]*.

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

Immune-Mediated Colitis

Immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology, can occur with OPDIVO treatment. Monitor patients for signs and symptoms of colitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents.

Withhold OPDIVO for moderate or severe (Grade 2 or 3) colitis. Permanently discontinue OPDIVO for life-threatening (Grade 4) or for recurrent colitis upon restarting OPDIVO *[see Dosage and Administration (2.4) in full Prescribing Information]*.

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

Immune-Mediated Hepatitis

Immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology, can occur with OPDIVO treatment. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or greater transaminase elevations, with or without concomitant elevation in total bilirubin. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis *[see Dosage and Administration (2.4) in full Prescribing Information and Adverse Reactions]*.

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

Immune-Mediated Endocrinopathies

Hypophysitis

Hypophysitis can occur with OPDIVO treatment. Monitor patients for signs and symptoms of hypophysitis. Administer corticosteroids at a dose of 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or greater hypophysitis. Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3) and permanently discontinue OPDIVO for life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.4) in full Prescribing Information]*.

Adrenal Insufficiency

Adrenal insufficiency can occur with OPDIVO treatment. Monitor patients for signs and symptoms of adrenal insufficiency during and after treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency *[see Dosage and Administration (2.4) in full Prescribing Information]*.

In Trials 1, 3, and 5 (n=761), less than 1.0% of OPDIVO-treated patients developed adrenal insufficiency.

Hypothyroidism and Hyperthyroidism

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

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

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

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus can occur with OPDIVO (nivolumab) treatment. Monitor for hyperglycemia. Administer insulin for type 1 diabetes and withhold OPDIVO in cases of severe (Grade 3) hyperglycemia until metabolic control is achieved. Permanently discontinue OPDIVO for life-threatening (Grade 4) hyperglycemia.

Immune-Mediated Nephritis and Renal Dysfunction

Immune-mediated nephritis, defined as renal dysfunction or ≥Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology, can occur with OPDIVO treatment. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, and administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper. If worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue OPDIVO. Permanently discontinue OPDIVO and administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) increased serum creatinine *[see Dosage and Administration (2.4) in full Prescribing Information and Adverse Reactions]*.

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

Immune-Mediated Rash

Immune-mediated rash can occur with OPDIVO treatment. Severe rash (including rare cases of fatal toxic epidermal necrolysis) occurred in the clinical program of OPDIVO. Monitor patients for rash. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for severe (Grade 3) or life-threatening (Grade 4) rash. Withhold OPDIVO for severe (Grade 3) rash and permanently discontinue OPDIVO for life-threatening (Grade 4) rash *[see Dosage and Administration (2.4) in full Prescribing Information]*.

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

Immune-Mediated Encephalitis

Immune-mediated encephalitis can occur with OPDIVO treatment. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. Evaluation may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for immune-mediated encephalitis *[see Dosage and Administration (2.4) in full Prescribing Information]*.

Across clinical studies of 8490 patients receiving OPDIVO as a single agent or in combination with ipilimumab, less than 1.0% of patients were identified as having encephalitis. In Trial 3, fatal limbic encephalitis occurred in one patient (0.3%) receiving OPDIVO after 7.2 months of exposure. OPDIVO was discontinued; corticosteroids were administered.

Other Immune-Mediated Adverse Reactions

Other clinically significant immune-mediated adverse reactions can occur. Immune-mediated adverse reactions may occur after discontinuation of OPDIVO therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting OPDIVO after completion of corticosteroid taper based on the severity of the event *[see Dosage and Administration (2.4) in full Prescribing Information]*.

The following clinically significant, immune-mediated adverse reactions occurred in less than 1.0% of patients receiving OPDIVO as a single agent or in combination with ipilimumab in Trials 1, 3, 4, 5, and 6 (n=1261): uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, and systemic inflammatory response syndrome.

Across clinical trials of OPDIVO as a single agent administered at doses of 3 mg/kg and 10 mg/kg the following additional clinically significant, immune-mediated adverse reactions were identified: motor dysfunction, vasculitis, and myasthenic syndrome.

Infusion Reactions

Severe infusion reactions have been reported in less than 1.0% of patients in clinical trials of OPDIVO as a single agent. Discontinue OPDIVO in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions.

In Trials 3 and 5, Grade 2 infusion reactions occurred in 1.0% (5/493) of patients receiving OPDIVO.

Embryofetal Toxicity

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

The data in the Warning and Precautions section reflect exposure to OPDIVO, as a single agent, for clinically significant adverse reactions in 1590 patients enrolled in Trials 1, 3, 5, 6, a single-arm trial in NSCLC (n=117), or an additional dose-finding study (n=306) administering OPDIVO as a single agent at doses of 0.1 to 10 mg/kg every 2 weeks *[see Warnings and Precautions]*.

The data described below reflect exposure to OPDIVO as a single agent in Trial 3, which is a randomized trial in patients with metastatic non-squamous NSCLC.

Metastatic Non-Squamous Non-Small Cell Lung Cancer

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

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

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

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

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

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

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

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

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

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

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

Immunogenicity

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

Of 639 patients who were treated with OPDIVO 3 mg/kg every 2 weeks and evaluable for the presence of anti-nivolumab antibodies, 73 patients (11.4%) tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay. Neutralizing antibodies against nivolumab were detected in five patients (0.8%). There was no evidence of altered pharmacokinetic profile or toxicity profile with anti-nivolumab binding antibody development.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to OPDIVO with the incidences of antibodies to other products may be misleading.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Contraception

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

Pediatric Use

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

Geriatric Use

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

Renal Impairment

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

Hepatic Impairment

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

OVERDOSAGE

There is no information on overdosage with OPDIVO.

PATIENT COUNSELING INFORMATION

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

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

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus *[see Warnings and Precautions]*.
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions]*.
- Rash: Advise patients to contact their healthcare provider immediately for rash *[see Warnings and Precautions]*.
- Encephalitis: Advise patients to contact their healthcare provider immediately for neurological signs or symptoms of encephalitis *[see Warnings and Precautions]*.
- Infusion Reactions: Advise patients of the potential risk of infusion reaction *[see Warnings and Precautions]*.
- Females of Reproductive Potential: Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions, Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose of OPDIVO *[see Use in Specific Populations]*.
- Lactation: Advise women not to breastfeed while taking OPDIVO *[see Use in Specific Populations]*.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

U.S. License No. 1713

1363787 Revised: November 2015

1506US1503692-07-01

Bristol-Myers Squibb

THE AMERICAN JOURNAL OF MANAGED CARE®

PUBLISHING STAFF

SENIOR VICE PRESIDENT OF OPERATIONS AND CLINICAL AFFAIRS
Jeff D. Prescott, PharmD, RPh

ASSOCIATE EDITORIAL DIRECTOR
Nicole Beagin

MANAGING EDITOR
Surabhi Dangi-Garimella, PhD

MANAGING EDITOR
Mary K. Caffrey

QUALITY ASSURANCE EDITORS
Maggie Shaw
Griselda Demassey

ASSOCIATE PUBLISHER
Justin T. Gallagher

DIRECTOR OF SALES
Sara Belanger

NATIONAL ACCOUNT MANAGER
Gil Hernandez

CONTROLLER
Jonathan Fisher, CPA

ASSISTANT CONTROLLER
Leah Babitz, CPA

ACCOUNTANT
Tejinder Gill

GROUP DIRECTOR, CIRCULATION & PRODUCTION
John Burke

DESIGNER
Gwen Salas

CORPORATE OFFICERS

CHAIRMAN AND CEO
Mike Hennessy, Sr

VICE CHAIRMAN
Jack Lepping

PRESIDENT
Mike Hennessy, Jr

EXECUTIVE VICE PRESIDENT AND GENERAL MANAGER
John Maglione

CHIEF OPERATING OFFICER AND CHIEF FINANCIAL OFFICER
Neil Glasser, CPA/CFE

PRESIDENT, MANAGED MARKETS, PHARMACY, AND RARE DISEASE
Brian Haug

CHIEF CREATIVE OFFICER
Jeff Brown

HUMAN RESOURCE DIRECTOR
Shari Lundenberg

Scan here to visit ajmc.com.

Michael J. Hennessy Associates, Inc.

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

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

GRANIX® (TBO-FILGRASTIM) Injection

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

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

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

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

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

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

Important Safety Information

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

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

For more information, visit GRANIXhcp.com.

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

TEVA Oncology

GRANIX®
(TBO-FILGRASTIM)
Injection

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

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

5.2 Acute Respiratory Distress Syndrome (ARDS)

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

5.3 Allergic Reactions

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

5.4 Use in Patients with Sickle Cell Disease

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

5.5 Capillary Leak Syndrome

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

5.6 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

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

6 ADVERSE REACTIONS

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

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

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

6.1 Clinical Trials Experience

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

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

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

Leukocytosis

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

Additional Adverse Reactions

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

6.2 Immunogenicity

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

7 DRUG INTERACTIONS

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

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

Animal Data

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

No case of overdose has been reported.

TEVA Oncology

Manufactured by:
Sicor Biotech UAB
Vilnius, Lithuania
U.S. License No. 1803

Distributed by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Product of Israel

GRX-40580 January 2015

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

Exciting New Treatments in Myeloma and a Focus on Healthcare Policy at the Annual ASH Meeting

The annual meeting of the American Society of Hematology (ASH) provides an excellent platform for experts in the field to share, discuss, and collectively shape the future of research and care for diseases of the blood. With a number of new and exciting drugs approved in 2015, the 57th annual meeting, held December 5-8, 2015, in Orlando, Florida, did not disappoint.

The highlight of the meeting was a hastily organized joint session by ASH and the FDA that, for the first time, saw participation by reviewers from the FDA's Office of Hematology and Oncology Products at the hematology meeting. The reviewers, and 2 clinicians associated with the development of these drugs, discussed 3 new products for multiple myeloma that were all approved just the month before the meeting.

As witnessed in the meeting last year, ASH shared its 2015 recommendations for healthcare providers who have been newly added to the *Choosing Wisely* initiative. This year, ASH's Choosing Wisely Task Force launched a first-of-its kind review of all existing Choosing Wisely recommendations to identify those published by other professional societies that are highly relevant and important to the practice of hematology. These included recommendations on imaging for suspected pulmonary embolism, thrombophilia testing in patients diagnosed with infertility, unnecessary routine complete blood count, unnecessary transfusions for iron deficiency, and appropriate use of imaging for cancer recurrence.

MIKE HENNESSY, SR

Along the lines of improving healthcare quality, experts discussed the importance of quality measures and pay-for-performance, and explained the relevance of these terms to clinicians in the current healthcare climate of value-based reimbursement. Another interesting session at this year's meeting included a discussion on alternate payment models, why providers should be in the know, and what payers expect of providers.

For a current update on other clinical meetings and news, please visit us at www.ajmc.com.

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

EDITORIAL MISSION

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

New Hematology Drugs: *Progress and Challenges Discussed at the 57th ASH Meeting*

SURABHI DANGI-GARIMELLA, PHD

An early session on the first day of the annual meeting and exposition of the American Society of Hematology, held December 5-8, 2015, in Orlando, Florida, saw presentations on the promise of newly approved hematology/oncology agents along with the challenges that clinicians face when treating patients with them. Physicians with clinical experience using these agents discussed the appropriate population, dosing, side effects, and adverse events presented by the real-world use of the molecules.


MIKKAEL A. SEKERS, MD, MS

Chaired by Mikkael A. Sekers, MD, MS, from the Cleveland Clinic, participants included Kenneth A. Bauer, MD, from the Beth Israel Deaconess Medical Center; Anjali S. Advani, MD, from the Leukemia Program at Cleveland Clinic; and Sagar Lonial, MD, Winship Cancer Institute, Emory University School of Medicine.

IDARUCIZUMAB

Bauer's presentation introduced idarucizumab (Praxbind), a humanized monoclonal antibody indicated for patients being treated with dabigatran (Pradaxa), for reversal of the anticoagulant effects of dabigatran. Developed by Boehringer Ingelheim Pharmaceuticals, idarucizumab is used in emergency surgery or urgent procedures and to protect against life-threatening bleeding. Preclinical studies have shown that idarucizumab protects patients from bleeding when treated with the direct oral anticoagulant (DOAC) dabigatran.


KENNETH A. BAUER, MD

"Idarucizumab, a fully humanized antibody fragment, or Fab, has high affinity specifically for dabigatran and has shown no nonspecific binding to other agents," said Bauer, echoing results presented at the meeting of the American Heart Association late last year.[1]

Presenting updates from the REVERSE-AD,[2] or Reversal Effects of Idarucizumab on Active Dabigatran study, which led to the drug's approval, Bauer said that the management of dabigatran-related major bleeding using reversal agents can prove challenging. REVERSE-AD included 90 patients treated with idarucizumab, who were divided into 2 cohorts. Group A included 51 patients who had uncontrolled bleeding with dabigatran, while those in group B were 39 patients who needed emergency surgery or procedure following dabigatran treatment. The patients were administered 5 g intravenous (IV) idarucizumab, back-to-back in 2 separate infusions lasting 0 to 15 minutes. Within minutes of administration, idarucizumab normalized either elevated dilute thrombin time (dTT) or elevated ecarin clotting time (ECT), the study reported.

"The primary endpoints of maximum percent reversal of the anticoagulant effect of dabigatran, based on central-lab assessment of dTT or ECT within 4 hours of idarucizumab," explained Bauer. "Secondary endpoints were cessation of bleeding in group A and hemostasis during procedure in group B."

Although dTT normalized in 98% of group A and 93% of group B patients, ECT normalized in 89% of group A and 88% of group B patients, Bauer showed. "Safety issues are a concern with idarucizumab," he said, including some thrombotic events observed within 3 days and 4 events later on. While there were no cases of hypersensitivity, the trial saw 18 deaths, 9 in each group. "But deaths were primarily related with comorbidities that these very sick patients suffered from," Bauer added

An ideal treatment strategy for the management of dabigatran complications, according to Bauer, includes:

- Discontinue or hold dabigatran treatment
- Supportive care (with IV fluids, packed red blood cells)
- Activated charcoal within 2 hours of treatment
- Localization management of bleeding site
- Administer idarucizumab

He then listed some challenges associated with using reversal agents with DOACs, including:

- Insufficient data on whether supportive measures suffice or whether invasive procedures may be necessary
- Quantitative assays for DOACs are not yet available

"For intracerebral bleeding, early presentation to a healthcare facility, prompt diagnosis, and prompt administration of an effective reversal agent [are] critical to improve outcomes," Bauer concluded.

BLINATUMOMAB

Introducing the case of an adult acute lymphoblastic leukemia (ALL) patient in her clinic, Advani explained that although overall survival (OS) for pediatric ALL patients is very encouraging, "novel approaches are needed for treating adult ALL patients. The 3-year OS for 759 adults enrolled in a Cancer and Leukemia Group study is low—it's an unmet need," said Advani. She explained that while 80% of ALLs are B-cell subtype, most are pre-B ALL, and that CD19 has been a particularly attractive target for new therapies that are being developed.


ANJALI S. ADVANI, MD

"Blinatumomab is unique in that it's an anti-CD19 antibody, but it is a bispecific T-cell engager antibody. Of the 2 arms of this antibody, one engages the B-lymphoblast and the other the anti-CD19 antibody," Advani said. So the molecule can act as a bridge, she explained. Blinatomumab (Blincyto) was approved late last year for the treatment of ALL.[3]

A major challenge, in Advani's opinion, is the need for continuous drug infusion with blinatumomab, a complication with treatment that arises due to the short half-life of the drug. Short-term IV infusion schedules with blinatumomab were disappointing, Advani said. Some early results with the drug found an 80% rate of complete response in patients on blinatumomab, she noted. A follow-up study published in *Lancet Oncology*[4] showed promising results in adult patients with relapsed or refractory B-precursor ALL. The trial, Advani said, recruited 189 patients who were Philadelphia chromosome negative (Ph-) and heavily pretreated; almost 70% had a bone marrow blast count that was ≥50%.


SAGAR LONIAL, MD

"While response rate was lower in this multicenter trial, it's important to note that these were more heavily pretreated patients," Advani said, explaining the results. Whereas a complete response was observed in 43% of patients, minimal residual disease response was high, observed in 82% of trial participants.

The most significant side effects of blinatumomab include fever, headache, and febrile neutropenia. Advani then pointed out several management issues with blinatumomab. The drug's short half-life necessitates a continuous infusion: 4 weeks on and 2 weeks off. This calls for a very compliant patient. In trials, bag changes are required every 48 hours, which can create logistical issues. The drug is expensive, too: $89,000 per month of therapy. Health plans need prior authorization for drug use. Patients may need hospitalization for at least 2 days. Neurologic toxicity is observed in about 50% patients; however, severe incidences are rare.

Advani said that she is part of a phase 2 study that is currently recruiting elderly ALL patients, who are either Ph+ or Ph-, for treatment with blinatumomab in combination with prednisone, vincristine, methotrexate, and 6-mercaptopurine, also known as POMP. "We have hopes of improving patient outcomes with this combination," she said.

"Blinatumomab is a new class of bispecific T-cell engaging antibodies with significant activity in B-ALL that can hopefully improve outcomes," Advani concluded.

PANOBINOSTAT

The last molecule, introduced by Lonial, was panobinostat, a histone deacetylase inhibitor (HDAC) approved earlier this year for the treatment of patients with multiple myeloma (MM).[5]

"It is very important to know how to use drugs once they have been approved," said Lonial, underscoring the importance of real-world experience with drugs. Some other drugs currently being developed in the HDAC inhibitor class include vorinostat, givinostat, ricolinostat, and romidepsin, Lonial said.

A unique feature of myeloma cells, according to Lonial, is that they continue with their normal function, unlike most other cancerous cells whose normal cellular functions are compromised. "Myeloma cells continue to produce antibodies, which can then be used as a biomarker to measure response," Lonial explained. He showed that while preclinical data with pano-

binostat, generated by various groups, has confirmed the drug's activity, preliminary data from animal models has shown antiosteoclast activity of panobinostat. The study published in *Blood* in 2013 by Richardson et al, presenting results from the PANORAMA 2 trial,[6] showed that panobinostat could resensitize refractory patients to a combination of bortezomib and dexamethasone, Lonial explained.

"[The] best responders, based on subgroup analysis, were patients with high-risk disease and those who had been heavily exposed to prior therapies, including bortezomib and IMiD," Lonial said. The major toxicities observed with panobinostat include diarrhea and fatigue (asthenia). While grade 3 or 4 diarrhea has been consistently observed across studies, the combination of panobinostat with bortezomib is what may be causing these grade 3 or 4 toxicities, Lonial clarified. "So there is a need for better partners with panobinostat, and our options include carfilzomib and ixazomib," which he said are currently being evaluated in the clinic. **EBO**

REFERENCES

1. Caffrey M. Idarucizumab reverses dabigatran but not other anticoagulants, session reports. *AJMC* website. http://www.ajmc.com/conferences/aha2015/idarucizumab-reverses-dabigatran-but-not-other-anticoagulants-session-reports. Published November 10, 2015. Accessed December 17, 2015.
2. Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373(6):511-520.
3. FDA approves Blincyto to treat a rare form of acute lymphoblastic leukemia [press release]. Silver Spring, MD: FDA; December 3, 2014. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm425549.htm.
4. Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2015;16(1):57-66.
5. Panobinostat. FDA website. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm435339.htm. Updated February 24, 2015. Accessed December 17, 2015.
6. Richardson PG, Schlossman RL, Alsina M, et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. *Blood*. 2013;122(14):2331-2337.

Novel Combinations in Multiple Myeloma and Lymphoma

MICHAEL R. PAGE, PHARMD, RPH, AND SURABHI DANGI-GARIMELLA, PHD

MULTIPLE MYELOMA

In a session on new agents and combination treatments for myeloma, Philippe Moreau, MD, from the University of Nantes, France, presented a subgroup analysis from the randomized phase 3 ENDEAVOR Study, during the annual meeting of the American Society of Hematology.

The ENDEAVOR study results, recently published in the *Lancet Oncology*,[1] demonstrated that the doublet of carfilzomib and dexamethasone (Kd) significantly improved progression-free survival (PFS) compared with bortezomib (BTZ) and dexamethasone (Vd) (median PFS, 8.7 vs 9.4 months; hazard ratio [HR], 0.53; 95% CI, 0.44-0.65; *P* <.0001) in relapsed multiple myeloma (RMM). The subgroup analysis compared Kd or Vd after first relapse versus 2 or more prior lines of therapy.

PHILIPPE MOREAU, MD

The randomized phase 3 study evaluated 929 adult patients with RMM who had received 1 to 3 prior lines of therapy. Patients were randomized 1:1 to Kd or Vd. Patients in the Kd arm received carfilzomib (30-min intravenous [IV] infusion) on days 1, 2, 8, 9, 15, and 16 (20 mg/m^2 on days 1 and 2 of cycle 1; 56 mg/m^2 thereafter) and dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23 of a 28-day cycle. Patients in the Vd arm received BTZ 1.3 mg/m^2 (IV or subcutaneously) on days 1, 4, 8, and 11 and dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle. Treatment continued until disease progression or unacceptable toxicity. The primary endpoint was PFS and secondary endpoints included overall survival (OS), overall response rate (ORR), duration of response, rate of grade 2 or higher peripheral neuropathy, and safety.

The analysis found median PFS for patients who had received 1 prior line was 22.2 months (95% CI, 17.7-not estimable [NE]) for Kd versus 10.1 months (95% CI, 8.8-12.7) for Vd (HR, 0.45; 95% CI, 0.33-0.61). Patients who had received at least 2 lines of therapy, however, did not respond as well to Kd: median PFS among these patients was significantly lower at 14.9 months (95% CI, 10.2-NE) and for Vd-treated patients it was 8.4 months (95% CI, 6.5-10.2). Additionally, the analysis found that prior exposure to either BTZ or lenalidomide reduced median PFS in both the Kd and Vd treatment groups. Similar trends were noted with ORR in these subgroups.

Grade 3 and greater adverse events (AEs) were significantly higher with Kd compared with Vd: 69.8% and 63.9%, respectively, in patients with 1 prior treatment, and 76.6% and 69.9%, respectively, in patients with at least 2 prior treatments. Grade 3 or higher hypertension, dyspnea, and cardiac failure were more common in the Kd group.

With these results, Moreau concluded that Kd treatment in patients with RMM yielded clinically meaningful improvement in PFS, regardless of the number of prior lines of therapy. "However, this improvement was more significant in patients who had received 1 previous line of therapy," he said. Further, the PFS benefit with either combination was recognized regardless of prior exposure to specific agents.

"Our results show that the combination of carfilzomib and dexamethasone has a favorable benefit-risk profile in RMM, irrespective of prior treatment, and this 2-drug combination should be considered in patients who have progressed on lenalidomide maintenance," Moreau proposed.

> **"Our results show that the combination of carfilzomib and dexamethasone has a favorable benefit-risk profile in [relapsed multiple myeloma], irrespective of prior treatment, and this 2-drug combination should be considered in patients who have progressed on lenalidomide maintenance."**
>
> —PHILIPPE MOREAU, MD

DIFFUSE LARGE B CELL LYMPHOMA

In a phase 2 open-label trial of bortezomib plus R-CHOP (rituximab, cyclophosphamide, doxorubicin [Hydroxydaunomycin], vincristine, and Prednisone) therapy, investigators tested whether the including bortezomib would improve response rates in patients with diffuse large B cell lymphoma (DLBCL) of the non-germinal center B cell (GCB) subtype.[2] Investigators randomized patients who were previously untreated to receive VR-CHOP (n = 95) or standard R-CHOP (n = 95). In both trial arms, patients received at least 6 cycles of therapy. Researchers evaluated primary and secondary endpoints of PFS and secondary endpoints of OS, ORR, complete response (CR), and safety. This study was powered to detect a 15 percentage point difference in response rate at 2 years with VR-CHOP versus R-CHOP. Patients were evaluated at the end of cycles 2 and 6 using a fluorodeoxyglucose (FDG) positron emission tomography scan and through computed tomography (CT) scan.

A total of 206 patients were randomized to receive treatment, with 103 patients in each arm of the trial. However, of the patients who actually received at least 1 dose of study medication (the modified intent-to-treat population), only 91 qualified for this population in the R-CHOP group versus 92 patients in the VR-CHOP group. Further reducing this number, the evaluable patients in each arm (R-CHOP and VR-CHOP) were 86 and 90, respectively.

In terms of demographic characteristics, patients had a median age of 64 years and population characteristics were evenly balanced across risk groups. Three-fourths of all patients had stage 3 or stage 4 disease upon randomization. Of patients receiving R-CHOP, 86% completed all 6 cycles of treatment, comparable to the 85% of patients receiving VR-CHOP for all 6 cycles. The median dose intensity in this trial was greater than 98% of the full therapeutic dose, indicating very few dose reductions due to AEs. Following at least 6 weeks of therapy, patients were followed for a median of 34 months.

No significant difference in PFS was observed between the 2 regimens. After 2 years of therapy, 78% of patients receiving R-CHOP and 82% of patients receiving VR-CHOP met the PFS endpoint (*P* = .611). In subanalyses of low- and high-risk groups, PFS curves were identical to those with high-risk or intermediate-/high-risk disease. Similarly, OS

(continued on **SP12**)

imbruvica®
(ibrutinib) 140mg capsules

YOU&i™ Support

www.youandisupport.com

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

Help Patients Enroll

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

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

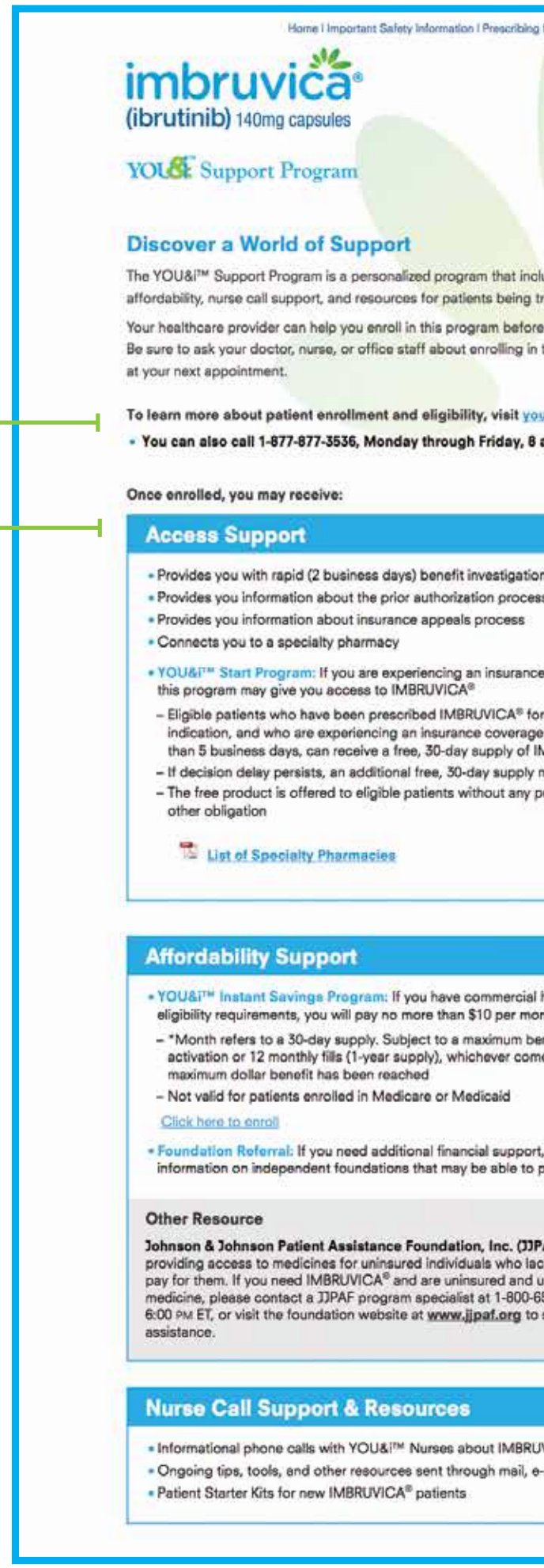
Access Support

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

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

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


imbruvica
(ibrutinib) 140mg capsules
Specialty Pharmacy Provider Network


Home | Important Safety Information | Prescribing

imbruvica®
(ibrutinib) 140mg capsules

YOU&i™ Support Program

Discover a World of Support

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

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

To learn more about patient enrollment and eligibility, visit you

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

Once enrolled, you may receive:

Access Support

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

List of Specialty Pharmacies

Affordability Support

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

Click here to enroll

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

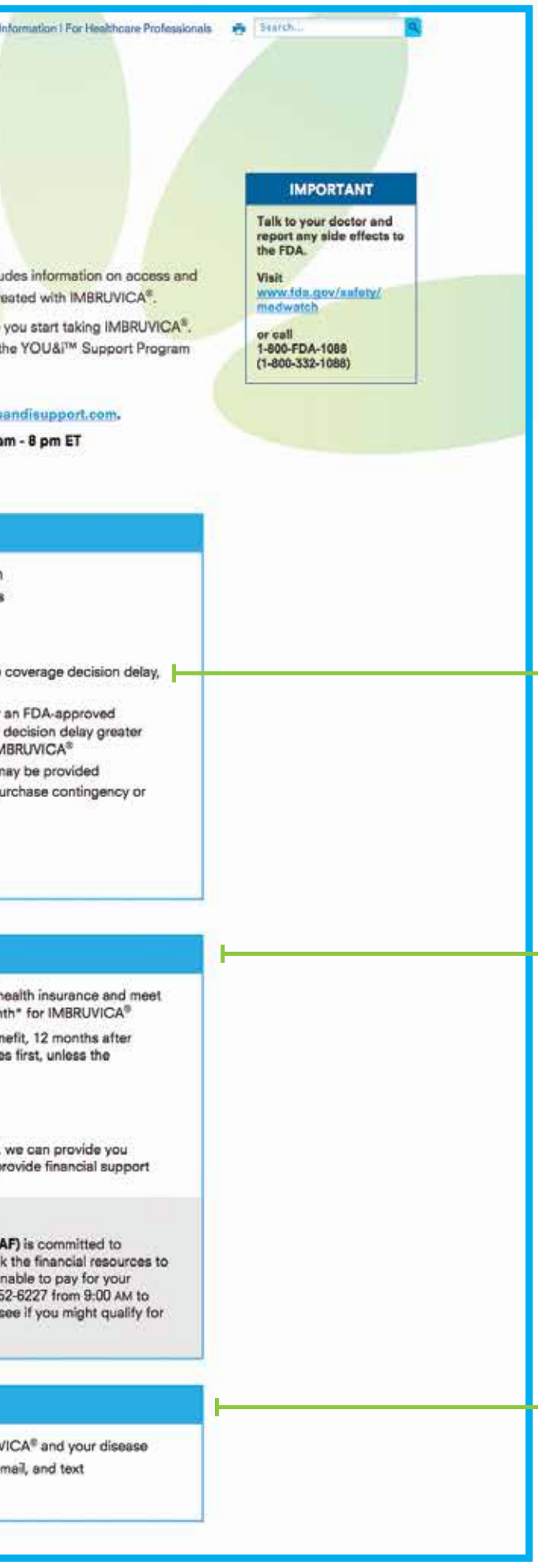
Other Resource

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

Nurse Call Support & Resources

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

Program Mapped!®



YOU&i™ Start Program

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

Affordability Support

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

Nurse Call Support & Resources

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

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

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

03/15 PRC-00962

pharmacyclics®

janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

(continued from **SP9**)

was unaffected, with 88% of patients receiving R-CHOP and 93% of patients receiving VR-CHOP surviving at the 2-year end point ($P = .78$). These negative results indicate no benefit to adding bortezomib to treatment of patients with DLBCL without the GCB genotype.

Although this negative finding may indicate that bortezomib is not effective in these patients, it is possible that the method of selection of patients (the Hans IHC algorithm) did not adequately select patients with the non-GCB genotype. In addition, it is possible that patients randomized in a prospective analysis (as in this study) selects out patients with very severe disease who tend to drop out of clinical trials. This bias in prospective studies versus retrospective studies may explain why retrospective studies show a benefit with bortezomib, whereas prospective studies do not.

In another prospective randomized controlled trial of bortezomib added to R-CHOP therapy in patients with DLBCL, researchers from the United Kingdom reported similarly negative results. This study, known by the acronym REMoDL-B, showed the results of treatment with targeted therapy for DBLCL based on a real-time gene expression profiling data.[3]

Rather than focusing solely on the non-GCB population, researchers separated patients into 3 groups: patients with the GCB genotype, the activated B cell (ABC) genotype, and patients with DLBCL who could not be categorized. In patients with the ABC genotype, the NF-kappa-B pathway is known to be constitutively active. Due to this constitutive activity, the goal of bortezomib therapy is inhibition of this pathway to improve outcomes in patients with the ABC genotype.

A total of 1085 patients were eligible for this study and were randomized to treatment. Of patients enrolled in the study, 248 had the ABC genotype, 477 had the GCB genotype, and 201 patients were unclassifiable. For 130 additional patients, screening failed for a variety of reasons, and 29 patients did not receive results due to technical equipment failures. Patients with both ABC and GCB genotypes and unclassifiable patients were randomized to receive R-CHOP or VR-CHOP, and baseline demographics in each group were generally well matched.

Across treatment groups, rates of AEs of grade 3 or higher severity were similar, and rates of neuropathy were broadly similar, with the exception of grade 3 or higher neuropathy, which was more common in the VR-CHOP arm than in the R-CHOP arm (3.0% vs 0.9%). CR rates as determined by CT scan were nearly equivalent in all groups treated, with response rates hovering around 60%. No significant differences were detected across groups, even after multiple subanalyses.

Over a median follow-up of 16.3 months, researchers observed 245 progression events and 138 deaths (12.7% of the population). Most of these deaths were the result of progressive disease. For the full population sample, PFS was 79.0% at 12 months and 71.7% at 24 months. Although the data from this study remains immature, the results are unpromising, with PFS curves for all patient subgroups that virtually overlap. These results confirm that real-time gene expression profile is possible in a clinical trial, with low failure rates due to equipment failure. However, addition of bortezomib to R-CHOP chemotherapy does not appear to affect rates of early treatment failure in patients with DLBCL of any subtype. **EBO**

REFERENCES

1. Dimopoulos MA, Moreau P, Palumbo A, et al; ENDEAVOR Investigators. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol.* 2015. pii: S1470-2045(15)00464-7.
2. Gonzalez-Barca E, Carillo E, Martin A, et al. Phase 2 randomized trial comparing 6 cycles of standard RCHOP chemotherapy vs 6 cycles of Brcap (bortezomib, rituximab, cyclophosphamide, adriamicine and prednisone) as first line treatment in young patients with poor prognosis diffuse large B-cell lymphoma (DLBCL): interim analysis. American Society of Hematology annual meeting website. https://ash.confex.com/ash/2015/webprogram/Paper82606.html. Accessed December 18, 2015.
3. Davies AJ, Caddy J, Maishman T, et al. A prospective randomised trial of targeted therapy for diffuse large B-cell lymphoma (DLBCL) based upon real-time gene expression profiling: the Remodl-B study of the UK NCRI and SAKK lymphoma groups. American Society of Hematology annual meeting website. https://ash.confex.com/ash/2015/webprogram/Paper86301.html. Accessed December 18, 2015.

Abundant Optimism at the ASH/FDA Joint Symposium on New Drug Approvals in Multiple Myeloma

SURABHI DANGI-GARIMELLA, PHD

"We have witnessed unprecedented progress in the treatment of multiple myeloma (MM). Things have moved very well, and most of this is because we now have a plethora of new drugs to support care pathways." These opening statements by S. Vincent Rajkumar, MD, of the Mayo Clinic in Rochester, Minnesota, summarized the objectives of a novel FDA-sponsored session at the end of the third day of the American Society of Hematology (ASH)'s annual meeting.

PAUL G. RICHARDSON, MD

Primary clinical reviewers from the FDA who reviewed applications for daratumumab (Darzalex), ixazomib (Ninlaro), and elotuzumab (Empliciti)—all approved in November 2015—discussed the safety and efficacy issues from the products' clinical trials and toxicity studies. Additionally, 2 clinicians who have extensive experience with these drugs in real-world settings shared their perspectives, focusing on combination therapies and sequencing.

Albert B. Deisseroth, MD, PhD, of the FDA's Office of Hematology and Oncology Products, served as moderator. "We are in the midst of a revolution in targeted drug therapies," Deisseroth said. "Three new treatments of MM were approved in just the past 3 weeks. To ensure that promising new products meet an unmet medical need, and are approved expeditiously, the FDA has introduced accelerated, fast-track, breakthrough, and priority approvals." Deisseroth pointed out that just in the last 3 years, 18 fast-track products were approved.

FDA PERSPECTIVE

Daratumumab

Barry W. Miller, MSN, CRNP, also from the FDA's Office of Hematology and Oncology Products, introduced daratumumab, a human CD38-directed monoclonal antibody that received breakthrough therapy designation in May 2013 and accelerated approval on November 16, 2015.[1] Miller was the primary clinical reviewer of the application.

"Daratumumab has been approved for the treatment of MM in patients who have received at least 3 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent, or those who are double refractory to a PI and an immunomodulatory agent," Miller said.

Miller showed that results from the MMY2002 trial were submitted for review. Daratumumab, he said, achieved its primary objective of overall response rate (ORR) when used in 106 patients who had received a median of 5 prior therapies. About 80% of these patients had received an autologous stem cell transplant. The duration of response, he showed, was 7.4 months.

S VINCENT RAJKUMAR, MD

"Daratumumab can, however, interfere with the determination of stringent and complete response," Miller said, adding that a few adverse events (AEs) associated with the drug include infusion reaction, fatigue, and nausea. "To avoid these reactions, patients could be pre-medicated with an antipyretic or a corticosteroid, and monitored," he added.

Ixazomib

Alexandria Schwarsin, MD, Office of Hematology and Oncology Products, FDA, and the primary clinical reviewer for ixazomib, introduced the drug, which was approved November 20, 2015.[2]

"The trial data that was reviewed was generated from a randomized, double-blind, placebo-controlled trial," Schwarsin said, "in relapsed or refractory MM patients who had undergone 1 to 3 prior treatment regimens." Patients refractory to lenalidomide or PIs were excluded from this trial.

Of the 2 trial arms, 224 patients with 1 prior therapy and 36 with 2 prior therapies were included in the ixazomib plus lenalidomide/dexamethasone (LenDex) arm, while 217 with 1 prior treatment and 145 with 2 prior treatments were included in the placebo plus LenDex arm. Prior therapies received by these patients included

bortezomib, carfilzomib, thalidomide, lenalidomide, melphalan, and stem cell transplantation. The median progression-free survival (PFS), which was the primary endpoint, was 20.6 months in the ixazomib arm versus 14.7 months in the placebo arm.

Major adverse reactions observed with the trial included diarrhea (more patients in the ixazomib arm had grade 3 diarrhea), constipation, and peripheral neuropathy, among others. Higher rates of grade 3-4 thrombocytopenia were observed with patients treated in the ixazomib arm, while grade 3-4 neutropenia was comparable between the arms. Ixazomib also resulted in a higher rate of cutaneous reactions.

"For patients with renal impairment, a reduced dose of the ixazomib is recommended," Schwarsin told the audience. She concluded that the FDA has approved ixazomib, in combination with lenalidomide and dexamethasone, for the treatment of patients with MM who have received at least 1 prior therapy.

Elotuzumab

Nicole J. Gormley, MD, Office of Hematology and Oncology Products, FDA, was the clinical reviewer for elotuzumab, approved November 30, 2015.[3]

"Elotuzumab has been approved in combination with lenalidomide and dexamethasone for patients with MM who have received 1 to 3 prior therapies," Gormley said.

The pivotal phase 3 trial of the drug evaluated elotuzumab in combination with LenDex versus LenDex alone, in relapsed or refractory MM patients who could previously have received lenalidomide. Co-primary endpoints of the trial (PFS and ORR) were evaluated by an independent review committee. The median PFS was 19.4 months in the elotuzumab arm compared with 14.9 months in the LenDex arm. Further, ORR was 78.8% in the elotuzumab arm compared with 65.5% for LenDex.

Sharing the list of AEs that increased with the addition of elotuzumab—including fatigue, pyrexia, diarrhea, and constipation—Gormley told the audience, "Opportunistic infections were also higher in the elotuzumab LenDex arm, primarily fungal infections and herpes virus infections." Two patients discontinued treatment due to hepatotoxicity, she said.

CLINICAL PERSPECTIVE

Rajkumar then took to the podium, telling the audience of the tremendous progress that the field of MM treatment has seen. He said that while alkylating agents may have been the only option a couple of decades back, "A plethora of new drugs have now been added to the armamentarium, and the list continues to expand."

"I will try to place a context with respect to diagnosis and staging and where the new approved drugs fall in MM therapy," Rajkumar told the audience.

Revisions within the International Myeloma Working Group criteria have changed the staging of MM, according to Rajkumar. "We now know that MM is a heterogeneous combination of 6 to 7 diseases and aggressiveness varies based on the kind of translocation observed in the disease."

> **"The new drug approvals have made an immense contribution to the armamentarium of drugs available for treatment. The question remains, however, how do you develop combinatorial treatment strategies for relapsed refractory patients?"**
>
> —PAUL G. RICHARDSON, MD

The initial therapy of LenDex overrode the use of melphalan, Rajkumar said. Introduction of bortezomib in the early 2000s prolonged PFS and overall survival (OS) compared with the standard of care LenDex. "And now, with the addition of other agents like carfilzomib, pomalidomide, [and] panobinostat, there are 22 potential treatment strategies within the NCCN guidelines, which, of course, adds to the confusion," he said.

"While bortezomib triplet is routinely preferred in frontline today, even in nontransplant patients, the treatment may be harsh for the frail and elderly population. So the LenDex doublet may still be recommended for them," Rajkumar explained. Providing a context for stem cell transplants in this scenario, he said that data presented at the ASH meeting showed early transplant could prolong OS.

The question now is, where can the newly approved agents be placed in these regimens? Emphasizing that the doublet therapy should be continued for the frail and elderly population of patients, Rajkumar thinks that the PI ixazomib could be combined with the doublet in the rest of the patients with standard risk who have trisomies. In the high-risk population, he recommends adding carfilzomib to the doublet or either of the monoclonal antibodies, daratumumab and elotuzumab.

Rajkumar insisted that we need to improve our clinical trial strategy so that decisions on choosing the triplet can be made more readily. He said that ongoing trials with the 3 news drugs will hopefully improve our understanding of using these drugs in maintenance therapy. He did point out the need for better endpoints than PFS (such as PFS 2, OS with higher type 1 error, or validated patient-reported outcomes or quality-of-life endpoints) for patients who are on maintenance therapy.

The second clinician expert was Paul G. Richardson, MD, from the Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, in Boston. He listed the following factors as those that influence treatment decisions in advanced MM:

1. Response to prior therapy; tolerability of prior therapy
2. Patient-related factors such as age, cytogenetic profile, and clonal heterogeneity
3. Aggressiveness and prognostic features of individual patients
4. Number of relapses and refractory disease

"The new drug approvals have made an immense contribution to the armamentarium of drugs available for treatment," Richardson said. The question remains, however, "How do you develop combinatorial treatment strategies for relapsed refractory (RR) patients?"

Richardson suggests a backbone of an immunomodulatory agent with bortezomib and then introducing chemotherapy or one of the newer agents. He believes that triplet therapy is better than doublet for RR patients.

Ixazomib, a first-in class oral PI, is a very well-tolerated oral agent, which provides a strong rational for using this agent, he said. "There might also be rationale in combining ixazomib with a histone deacetylase inhibitor like panobinostat in RR MM patients," Richardson said. All 3 drugs could be readily integrated in the treatment plans of patients with relapsed disease, he pointed out. **EBO**

REFERENCES

1. Dangi-Garimella S. Daratumumab approval yields the first monoclonal antibody, and another option, in multiple myeloma. *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 December 7, 2015.

2. Inman S. FDA approves Ixazomib for relapsed multiple myeloma. *OncLive* website. http://www.onclive.com/web-exclusives/fda-approves-ixazomib-for-relapsed-multiple-myeloma. Published November 20, 2015. Accessed December 18, 2015.

3. Dangi-Garimella S. FDA's decision on elotuzumab further expands options in multiple myeloma. *American Journal of Managed Care* website. http://www.ajmc.com/newsroom/fdas-decision-on-elotuzumab-further-expands-options-in-multiple-myeloma. Published November 30, 2015. Accessed December 7, 2015.

Experts Share Concepts of Quality Measures and Pay-for-Performance With Hematologists

SURABHI DANGI-GARIMELLA, PHD

Quality measurement, public performance reporting, and pay-for-performance have rapidly translated into established processes in the delivery, assessment, and evaluation of medical care in the United States, accelerated by the Affordable Care Act and CMS' proposed transition to value-based reimbursement. On the first day of the annual meeting of the American Society of Hematology, experts discussed these measures and what they would mean for a practicing hematologist in the coming years.

Some of the questions that were explored in this session included:

- Are current quality programs heading in the right direction?
- Can quality measures really help physicians improve patient care?
- Are quality measures even more harmful than helpful? Does pay-for-performance work?


ANDREW RYAN, PHD, MA

During her talk, "Quality Measures, Quality Reporting, and Value-Based Remuneration: How Did We Get Here and Where Are We Going?" Helen Burstin, MD, MPH, of the National Quality Forum (NQF), said, "As we move toward the new world of value-based payments, we really need to understand how did we get here and where we are going with these measures?"

The federal government, Burstin explained, came up with a National Quality Strategy based on the premise of better care, healthier people and communities, and smarter spending. These are the national priorities, and the goals for value-based reimbursement are based on these principles. "The push to population health in communities is a big area that needs prioritizing. The move from volume to value is a sea change, and there's significant growth expected in the move from fee-for-service (FFS) linked to quality payments and alternative payment models. By 2018, we expect 50% adoption of alternate payment models and a 90% FFS-quality link is expected," said Burstin. The question remains, though, whether we are ready for this move and have the tools to bring about this change, she said.


HELEN BURSTIN, MD, MPH

There are of course challenges to be surmounted, including tensions in measurement, according to Burstin, which include:

1. While outcomes measures are included to deduce accountability, process measures are primarily used for quality improvement.
2. The measurement burden for providers and clinicians creates the need for developing more comprehensive measures.
3. While the need is primarily for system-level measurements, individual clinician-level measurements are being set by the Medicare Access & CHIP Reauthorization Act of 2015.

Limited set of core measures (need metrics to meet needs of each specialty).

As we plan to move away from process-based–to outcomes-based measures, there's a need to think of modifying processes that can improve outcomes. A major move in the healthcare field, Burstin said, is the integration of patient-reported outcomes (PROs) with quality measures. "But these measures are riddled with challenges—they are not widely used in practice, more-so in clinical trials," and we don't have a method yet to aggregate PROs, she added.

Burstin listed the following challenges commonly faced when utilizing PROs:

- Persistent measurement gaps
- Potential for unintended consequences
- Alignment and harmonization of measures
- Complex measurement science issues

Outcomes measures, themselves, have their limitations, said Burstin, including, but not limited to:

- Patient selection can lead to differences across physician or hospital population (risk adjustment)
- Small sample size or event rate
- Longer-term outcomes may be difficult to track
- Ideal outcomes may not be achievable

Risk adjustment, she believes, is a significant challenge to surmount due to factors that are difficult to control for, including genetic characteristics, demographic characteristics, clinical factors, health-related behaviors, and psychosocial behaviors.

Burstin explained that NQF is working with health plans and CMS in an attempt to standardize and avoid "me too" measures. "This would help overcome variation and align the innumerable measures currently used in practice," she said. There are separate measures at the federal-programs, health-plans, and state-programs levels, in addition to individual provider-generated measures and ratings. All of these separate measures need to be evaluated and aligned to avoid overlap and unnecessary burden, she said.

"The push to population health in communities is a big area that needs prioritizing. The move from volume to value is a sea change, and there's significant growth expected in the move from fee-for-service (FFS) linked to quality payments and alternative payment models. By 2018, we expect 50% adoption of alternate payment models and a 90% FFS-quality link is expected."

—HELEN BURSTIN. MD, MPH

"The purpose of measurement is to improve healthcare quality, and we need to understand that they are the means to an end," said Burstin.

She ended with the following quote which has been attributed to Albert Einstein: "Not everything that can be counted counts, and not everything that counts can be counted."

According to Andrew Ryan, PhD, MA, from the department of Health Management and Policy at the University of Michigan, currently, the primary platform for measuring quality is the Physician Quality Reporting System (PQRS). "A majority of the 280 measures are related to clinical process performance. These measures are in use for hematology." He informed the audience that PQRS is now moving toward penalizing physicians for not reporting to PQRS.

Several studies have provided evidence of cost reduction, Ryan said, such as the hospital readmission reduction program, which has shown a significant decrease in readmissions. "However, public reporting has not improved outcomes or impacted consumer choice," which has been a trend observed across the board with several models, Ryan explained.

One reason for this, he pointed out, might have been the inclusion of both inpatient and outpatient data by hospitals, rather than inpatient data alone, Ryan said, adding, "The validity of many performance metrics are questionable, along with disparities in payments from hospital incentive programs."

He concluded his talk with several futuristic questions:

- Are PQRS measures taking us where we want to go?
- What is the role of hematologists in the larger system of accountable care?
- How should drug pricing and costs be accommodated in value-based payment systems?
- What is the model for an ideal accountability system for individual hematology practices and individual clinicians?

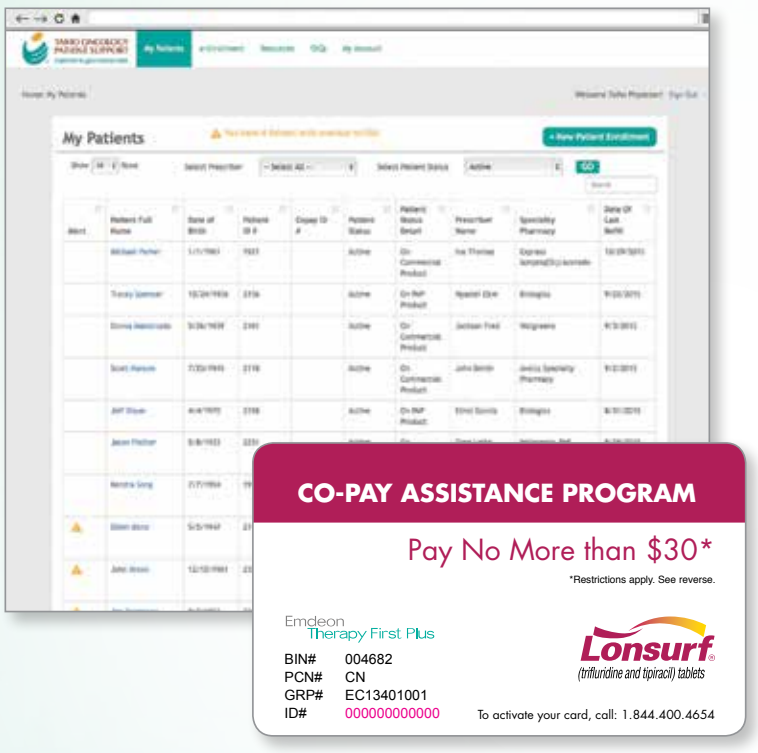
These are just a few of the open-ended questions that we hope will be answered over the next few years, as we see increasing adoption of these measures and models in clinical practice. **EBO**

TAIHO ONCOLOGY PATIENT SUPPORT

A partner in your cancer care.

Getting Patients Access to Treatment Can Be Challenging—**WE CAN HELP**

Taiho Oncology Patient Support complements the care you provide by offering customizable services that help with access and reimbursement for LONSURF® (trifluridine and tipiracil). We strive to make this critical step in your patients' treatment as simple as possible.



- **Benefit Investigations**
- **Prior Authorization and Appeals Assistance**
- **Specialty Pharmacy Rx Coordination**
- **Co-pay Support**
- **Patient Assistance Program**
- **Alternate Funding Support**
- **Personalized Nurse Support 24/7**
- **Online Provider Portal**

Enrollment is easy and convenient, both online and by phone

To learn more, visit
www.TaihoPatientSupport.com
and access the provider portal

Call our Resource Center toll free at
(844) TAIHO-4U [844-824-4648]
Monday through Friday, 8 AM – 8 PM ET

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.

How Do You Develop, and Successfully Incorporate, PROs in Hematology? Experts Chime in at ASH

SURABHI DANGI-GARIMELLA, PHD

A patient-reported outcome (PRO) is defined as the measurement of a patient's perception of a health condition and its treatment. A session on PROs and the importance of embracing the patient perspective in healthcare delivery witnessed a healthy discussion between a developer of these tools, a representative from the FDA who reviews these tools when used by drug developers, and a clinician who is the end-user of PROs in clinical practice. The panel was part of an educational session on Patient-Reported Outcomes in Hematology at the annual meeting of the American Society of Hematology.


DAVID CELLA, PHD

TOOL DEVELOPMENT

David Cella, PhD, from the Feinberg School of Medicine, Northwestern University, began the session, introducing The Science behind Developing a Patient-Reported Outcome Measure. Cella has been a pioneer in developing the Patient Reported Outcomes Measurement Information System (PROMIS),[1] which has seen widescale adoption in clinical practice. PROMIS is a National Institutes of Health (NIH)-funded measurement system that uses item response theory and provides researchers and clinicians the ability to determine PROs using precise and reliable tools.


JULIE A. PANEPINTO, MD, MSPH

Although Cella is involved in developing these outcomes measures across a range of therapeutic areas, he geared his talk to present the hematology context, outlining fatigue as an indexed symptom for patient-reported outcomes measures (PROMs), the promise of PROMs, and where he sees the future for these measures.

"There's value in asking systematic questions on patient outcomes. A series of endpoints, including tumor response, progression-free survival (PFS), and disease progression, which are commonly used as outcomes measures, may not always relate with overall survival (OS)," Cella said. "However, if we place a value on tumor response and PFS that makes sense to people, including the patients' treatment experience can significantly contribute to the value proposition of a regimen," he explained.

Providers can gather outcomes such as disease symptoms, side-effect burden, and tolerability throughout the treatment. These measures may be strongly associated with patient preference. However, in order to help patients make informed treatment decisions, there's a need to assess these measures through well-controlled studies, Cella said. It is important to realize that "Treatment benefit can be measured as a combination of treatment efficacy and treatment toxicity," he added.

Explaining fatigue as a therapeutic index, Cella talked about 3 well established international prognostic scoring systems: WHO-classification-based Prognostic Scoring System (WPSS), the International Prognostic Scoring System (IPSS), and the IPSS-revised. He then shared data from a recent paper in *Lancet Oncology*2 that evaluated self-reported fatigue in patients with myelodysplastic syndrome as an outcomes measure for OS, beyond IPSS. The researchers found that self-reported fatigue provides prognostic information for survival, independent of the gold-standard classifications, creating a case for fatigue to be included in routine diagnostic investigation in clinical trials. "However, what we are currently lacking is a single metric to standardize measures like fatigue—1 gold standard like blood pressure," said Cella.

That's how the PROMIS trial came about, he explained—PROMIS is domain-specific, not disease specific. A domain is the specific function, feeling, or perception that you want to measure, and it includes physical, social, and mental health measures. Each domain, such as fatigue, is measured using multiple "item banks," explained Cella. The data can be collected through survey questions or computerized adaptive testing or CAT—an adaptive, response-based tool.

Another patient-reported, self-assessment tool that Cella introduced is HealthMeasures[3]; a trans-NIH [National Institutes of Health] cooperative agreement that includes PROMIS, ASCQ-Me, NIH Toolbox, and Neuro-QoL.

"The future is in developing common standardized metrics to map out instruments like PROMIS, such as the PROsetta stone,[4] which can help link scores on 2 different measures," concluded Cella.

REGULATORY ROLE

So do PROs find a place in the regulatory world? Can they contribute to the drug approval process? Virginia E. Kwitkowski, MS, ACNP-BC, from the Division of Hematology Products, FDA, addressed these questions. With a focus on hematology, Kwitkowski described the advances in the assessment of PROs in clinical trials and provided an overview of regulatory issues to consider when using PROs in drug development.

Kwitkowski said, "An improvement in the way patients feel and function can also be considered evidence of their performance and be used as an outcome measure. Regulators do want PROs!" However, with respect to supportive care products that are developed to mitigate toxicity, evidence should support that patients are not being harmed, she said.

Pointing to the difference between the regulatory authorities in Europe versus the United States, Kwitkowski explained that contrary to regulators in Europe who do consider the impact of drug cost on the healthcare system as a whole prior to approval, the FDA is prevented from doing so. In 2009, the FDA generated guidance[5] for the industry on using PROs to support labeling claims, said Kwitkowski, "But flexibility and judgement are vital to meet regulatory questions."


VIRGINIA E. KWITKOWSKI, MS, ACNP-BC

In her opinion, existing issues with PROs in hematology/oncology include:

1. Historical assessment with static-global health related quality-of-life instruments
2. Rare, randomized blinded trials
3. Need for a modular approach

Explaining a roadmap developed by the FDA[6] for PRO measurement in clinical trials, Kwitkowski highlighted the salient features of the roadmap:

1. Understanding the disease or condition
2. Conceptualizing treatment benefit
3. Selecting/developing the outcome measure

Kwitkowski informed the audience that the FDA is very open to an exchange of ideas with drug developers on developing these PRO tool measurements, outside of a drug application.

"We are encouraged that so many stakeholders are interested in PROs in drug development. The FDA staff are actively working with stakeholders to help integrate PRO-CTCAE [Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events] in drug development. But a modular approach is recommended here," Kwitkowski said.

CLINICAL APPLICATIONS

The end-user of these very informative tools are oncologists and other healthcare providers who regularly interact with patients and help them make informed decisions on treatment choices. A big proponent of the use of PROs in clinical decisions is Julie A. Panepinto, MD, MSPH, an oncologist at The Medical College of Wisconsin/Children's Research Institute of the Children's Hospital of Wisconsin, Milwaukee.

Panepinto told the audience, "We don't know what patients are really doing outside of the clinic or the office visit," underscoring the importance of understanding patient behavior and functionality once they leave the clinic. She pointed to several studies that have shown that providers are not adept at estimating how patients function, especially psychosocial functions and pain management. "Additionally, there is evidence to show that there's significant discordance in not just the patient's PRO assessment, but also in the clinical documentation of these PROs," Panepinto said. "So we don't just not understand patient outcomes, we are not good at documenting it either."

Adapting to gathering PROs in the clinic, practices have come up with their own unique ways, Panepinto explained, showing examples of digital devices that are used. Computer kiosks, iPhones, or tabs can all be tools that can be used to collect PROs. Databases like MyCHart and REDCap can then help assemble this data, she said.

The underlying question remains, "Why collect PROs?" PROs can help a care team understand how patients are functioning. They can also help patients understand how they are performing relative to other patients like them who may be receiving similar treatment, Panepinto explained. "This information can significantly impact decision support in disease and therapy. While promoting patient-centered care, PROs can improve patient functioning and help tailor therapy to meet individual needs."

The field is now moving towards real-time incorporation of PROs in a clinical

setting to inform and adapt provider decisions on care. One such study examined the feasibility of PRO assessment via the Patient Reported Outcomes Measurement Information System-Computerized Adaptive Testing within pediatric hematology, oncology, and bone marrow transplant clinic settings.[7] Despite some technical barriers, the study ascertained that it was feasible to integrate PROs in the clinical setting in real time.

"PROs can greatly contribute to performance improvement. Healthcare systems can use PROs to track and improve delivery system performance, and more importantly, they can have a significant impact on improving population health," Panepinto said. **EBO**

REFERENCES

1. PROMIS. NIH website. http://www.nihpromis.org/?AspxAutoDetectCookieSupport=1#5. Accessed December 20, 2015.
2. Efficace F, Gaidano G, Breccia M, et al. Prognostic value of self-reported fatigue on overall survival in patients with myelodysplastic syndromes: a multicentre, prospective, observational, cohort study. *Lancet Oncol.* 2015;16(15):1506-1514.
3. HealthMeasures: transforming how health is measured. Healthmeasures website. http://www.healthmeasures.net/. Accessed December 20, 2015.
4. PROsetta Stone: linking patient-reported outcome measures. Prosetta Stone website. http://www.prosettastone.org/Pages/default.aspx. Accessed December 20, 2015.
5. Guidance for industry. Patient-reported outcome measures: use in medical product development to support labeling claims. FDA website. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf. Published December 2009. Accessed December 20, 2015.
6. Patient-focused outcome measurement in clinical trials. FDA website. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/UCM370174.pdf. Accessed December 20, 2015.
7. Myrvik MP, Beverung LM, Panepinto JA, et al. Integration of electronic patient-reported outcomes (ePROs) into pediatric clinic settings across hematology/oncology/bone marrow transplant. *Clin Pract in Pediatr Psychol*. 2014;2(1):39-49.

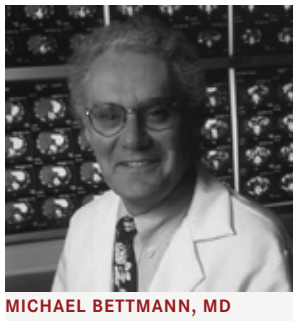
ASH Leverages Recommendations From Other Medical Organizations, Advising Hematologists to Choose Wisely

SURABHI DANGI-GARIMELLA, PHD

Choosing Wisely is a national medical stewardship campaign led by the ABIM Foundation. Multiple professional medical organizations now provide relevant recommendations on ways to avoid high utilization of unnecessary tests and treatments. Following-up on last year's list,[1] the American Society of Hematology (ASH)'s *Choosing Wisely* Task Force launched a first-of-its kind review of all existing *Choosing Wisely* recommendations to identify those published by other professional societies that are relevant and important to the practice of hematology, said Lisa Hicks, MD, from St. Michael's Hospital, University of Toronto, and the chair of the task force. The 13 hematologists on the task force chose the top 5 of 380 recommendations listed by 70 other societies for presentation at ASH. Each recommendation was introduced by a member of the task force.


LISA HICKS, MD

Using a rigorous methodology, the ASH *Choosing Wisely* Task Force scored 400 recommendations for relevance and importance over a series of iterations, resulting in this list of items deemed especially useful for hematologists. As with past ASH lists, harm avoidance was once again established as the campaign's preeminent guiding principle, with cost, strength of evidence, frequency, relevance, and impact serving as additional factors.


MICHAEL BETTMANN, MD

"The *Choosing Wisely* initiative is a high visibility campaign that has increased awareness of overutilization in medicine, and at ASH we believe there is a potential for even greater impact when societies share information and work together to accomplish the same goals," said Hicks. "ASH encourages all medical groups to follow its lead by examining other *Choosing Wisely* lists to find applicable recommendations that will improve quality of care and avoid harm from unnecessary tests and treatments."

"ASH has shown tremendous leadership by identifying additional *Choosing Wisely* recommendations relevant to hematologists and creating new ways of disseminating this important information to their members," said Richard Baron, MD, President and CEO of the ABIM Foundation. "By increasing awareness and understanding of what tests and treatments may be overused or unnecessary across all specialties, we'll help clinicians be better prepared to join their patients in these critical conversations about their care," Baron said.

1. **Don't image for suspected pulmonary embolism (PE) without moderate or high pre-test probability of PE.** Recommended by the American College of Radiology.

This recommendation was introduced by Michael Bettmann, MD, a radiologist affiliated with the Bowman Gray School of Medicine of Wake Forest University.

"For any test that is ordered, we have to assess the risk-benefit ratio, and it's especially important with pulmonary embolism," said Bettmann. Based on a review of available evidence, the task force recommends to avoid imaging for suspected PE without moderate to high pre-test probability. "Patients with low-risk can be safely excluded," said Bettmann.

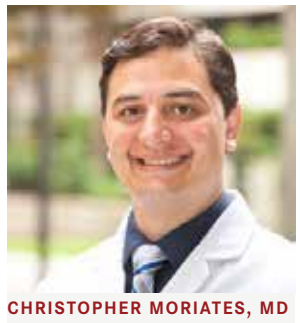
2. **Don't routinely order thrombophilia testing on patients undergoing a routine infertility evaluation.** Recommended by the American Society for Reproductive Medicine.

This recommendation was introduced by Shannon Bates, MDCM, MSc, FRCP(C), a hematologist at McMaster University.

"Nearly 15% couples may receive an infertility evaluation. Considering this relatively high number, there needs to be a clear association of thrombophilia and infertility or failure of assisted reproduction in these couples," insisted Bates.


SHANNON BATES, MDCM, MSc, FRCP(C)

Several population-based studies have found that thrombophilia is associated with infertility, resulting in couples being referred to in-vitro fertilization, said Bates, and an association between thrombophilia and failure of assisted reproduction has also been shown. "However, 2 large cohort studies have shown no association between, Factor V Leiden- or prothrombin gene mutations and assisted reproduction failure or infertility," she said. Mutations in Factor V and in the prothrombin gene have been known to result in thrombophilia.


CHRISTOPHER MORIATES, MD

Bates also drew attention to the use of low molecular weight heparin (LMWH) treatment in assisted reproduction. "Thrombophilia is not a predictor of who will benefit from LMWH treatment with respect to assisted reproduction. There is no consistent evidence showing association between thrombophilia and assisted reproduction or infertility," said Bates, reminding the audience that LMWH treatment is not benign and could have adverse effects.

3. **Don't perform repetitive complete blood count and chemistry testing in the face of clinical and lab stability.** Recommended by the Society for Hospital Medicine and Adult Hospital Medicine.

This recommendation was introduced by Christopher Moriates, MD, assistant clinical professor in the Division of Hospital Medicine at the University of California, San Francisco.

"Ordering complete blood counts (CBCs) has become a ritual for most of us, which we now know is unnecessary," Moriates said. Critically ill patients, he said, do not have the bone marrow reserve or erythropoietin drive to compensate for iatrogenic blood loss. To add to that are the risks of phlebotomy. It's not economical either, he explained, considering laboratory tests are not individually reimbursed and ordering too many unnecessary CBCs can be a loss to the hospital. "Disposing the biohazard waste of the blood samples is another avoidable cost," Moriates said.

So what are the options? Moriates assured the audience that there is evidence indicating that reducing the frequency of CBC does not result in adverse downstream effects, as is feared. "Multiple studies have shown that there's no difference in readmission rates, length of stay, rates of adverse events, etc. by reducing unnecessary daily laboratory tests."

4. **Don't transfuse red blood cells for iron deficiency without hemodynamic instability.** Recommended by the American Association of Blood Banks.

This recommendation was introduced by Jeannie Callum, MD, FRCPC, from the Sunnybrook Research Institute.

"The wise options for a patient in the emergency department (ED), who has iron deficiency, are either oral iron or

an intravenous (IV) infusion," said Callum. While oral iron is cheap, it causes GI disturbances, which are responsible for 50% adherence rates. Oral iron, however, is as effective as IV iron in terms of heme response at 6 to 8 weeks, she explained. But unnecessary blood transfusion is often used to compensate a person's iron deficiency, Callum said. "Research has shown that 20% of blood donors are iron deficient…so that's another ethical challenge, at least for me."

Callum directed the audience to a podcast that encourages cautious use of transfusions, and explains why IV iron might be a much better option for certain subsets of ED patients.[2]

5. Avoid using positron emission tomography (PET) or PET-CT scanning as part of routine follow-up care to monitor for a cancer recurrence in asymptomatic patients who have finished initial treatment to eliminate the cancer unless there is high-level evidence that such imaging will change the outcome. Recommended by the American Society of Clinical Oncology.

GARY LYMAN, MD, MPH

This recommendation was introduced by Gary Lyman, MD, MPH, co-director of the Hutchinson Institute for Cancer Outcomes Research.

"Until high-level evidence demonstrates that routine surveillance with PET/PET-CT prolongs life or promotes well-being, they should not be regularly performed."

CT scans expose patients to small doses of radiation, Lyman said. Although the clinical implications of these doses may not be significant, the cost implications definitely are.

Lyman concluded that high-quality evidence supporting the routine use of intensive surveillance to improve survival or enhance quality of life is lacking and he pointed out that professional organizations like ASCO, ESMO, and NCCN do not include surveillance PET in disease-specific guidelines. **EBO**

REFERENCES

1. Caffrey M. ASH presents second round of tests, treatments to question under Choosing Wisely initiative. *AJMC* website. http://www.ajmc.com/focus-of-the-week/1214/ash-presents-second-round-of-tests-treatments-to-question-under-choosing-wisely-initiative. Published December 9, 2014. Accessed December 20, 2015.

2. Episode 65-IV iron for anemia in emergency medicine. Emergency Medicine cases website. http://emergencymedicinecases.com/iv-iron-for-anemia-in-emergency-medicine/. Accessed December 20, 2015.

HEALTH OUTCOMES

Importance of Patient-Reported Outcomes and Quality-of-Life Measures in Myeloid Disease

SURABHI DANGI-GARIMELLA, PHD

Patients' assessment of their disease and treatment symptoms can significantly impact outcomes, potentially due to adherence issues. To date, adequately validated measures for patient-reported disease and treatment-related symptom burden in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are scarce. Identifying this gap, scientists at MD Anderson Cancer Center developed a short, valid, reliable patient-reported outcomes measure (PROM) of symptoms and symptom burden experienced by patients with AML and patients with MDS. The results from this study were consolidated in a poster that was presented at the annual meeting of the American Society of Hematology.[1]

A total of 152 patients with AML and 97 patients with MDS recruited to this study twice rated the 13 core symptom items (pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, trouble remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness and tingling), 6 proposed AML/MDS symptom items (muscle weakness, malaise, fever, headache, diarrhea, skin problems), and 6 interference items (general activities, mood, work, relations with others, walking, and enjoyment of life) on a 0-to-10 scale (0 = not present or no interference; 10 = as bad as can be imagined or complete interference), 1 to 2 days apart. Patient clinical and demographic information was collected from medical records and analyzed using descriptive statistics.

The study found that both groups of patients endorsed similar symptoms and the means of the 4 final AML/MDS symptoms were not significantly different between the groups, which led the authors to conclude that the lack of symptom recognition by patients with AML or MDS can lead to inadequate symptom management, interfere with patient ability to function and enjoy life, and impact the tolerability of and adherence to treatment regimens. The authors feel that their questionnaire, a PROM, is sensitive because it could recognize significant differences in symptom severity between AML inpatients and MDS outpatients.

Lead author Loretta A. Williams, PhD, RN, MSN, assistant professor in the Department of Symptom Research at MD Anderson Cancer Center, told *Evidence-Based Oncology*, "We were not sure that a single instrument would be appropriate for both AML and MDS. We were glad that while the instrument is sensitive to differences in severity of symptom burden between the 2 diseases, the same set of symptoms was appropriate for both." She sees potential for this PROM to be used by pharmaceutical companies in clinical trials of leukemia therapy because it was developed using the FDA guidance for patient-reported outcomes for labeling indications.

Some of the treatments used in patients with AML and MDS—many of whom are in their 60s and 70s—are harsh, and choosing these treatments for older patients can be a difficult decision, considering their impact on the patient's quality of life (QoL). In the absence of curative treatment, improving the patient's QoL holds importance. With this objective, researchers from the Moffitt Cancer Center compared QoL between groups receiving intensive therapy, nonintensive therapy, and supportive care, the results of which were also presented in the same session as the first study.[2]

Eighty-five patients diagnosed with high-risk MDS or AML, 60 years and older, were recruited at Moffitt Cancer Center between December 2013 and April 2015. Forty-six patients received intensive therapy, 34 received nonintensive therapy, and 5 received supportive therapy. The outcomes measure for QoL, Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu), established the following goals:

- Compare the difference in QoL scores measured by the FACT-Leu version for intensive chemotherapy, nonintensive therapy, and supportive care within 7 days of new treatment or the decision to pursue supportive care 1 month or later.
- Determine QoL predictors of AML and high risk MDS from age, comorbidity, fatigue, and diagnosis.
- Test the moderating effect of treatment with age, comorbidity, and fatigue on QoL.

The authors observed that the intensive-treatment group had significant improvements in their QoL scores at 1 month post treatment ($P = .04$). Considering the predictors of QoL, a significantly negative correlation was recorded between fatigue and QoL ($r = -0.693$, $P < .001$), indicating that QoL decreased with an increase in fatigue. However, the QoL scores for age, comorbidity, and fatigue were not moderated by treatment.

The authors concluded that the most intensive treatment improved QoL scores at 1 month and that fatigue is a significant predictor of QoL in this patient population. They suggest further studies with a larger, more diverse sample to explore the relationship between treatment approaches and QoL, in addition to intervention studies in AML and high risk MDS that would emphasize fatigue management.

Lead study author Sara M. Tinsley, PhD, ARNP, AOCN, from the Moffitt Cancer Center, wrote in an e-mail to *Evidence-Based Oncology*, "In our practice at Moffitt, we discuss various treatment options and their most common side effects, with very limited QoL data to guide our discussions. We discuss risk-to-benefit ratio, with the risk of death from treatment and the benefit of prolonged survival. From our preliminary findings, we can also inform patients that treatment with intensive treatment can improve their QoL at 1 month post treatment." Tinsley hopes that the findings of their study will inform decision making and lead to more longitudinal evaluation of QoL in patients with high-risk MDS and AML. **EBO**

REFERENCES

1. Williams LA, Garcia-Gonzalez A, Ahaneku HO, et al. A patient-reported outcome measure for symptoms and symptom burden of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). American Society of Hematology website. https://ash.confex.com/ash/2015/webprogram/Paper81364.html. Accessed December 18, 2015.

2. Tinsley SM, Small BJ, Lancet JE, et al. What is the impact on quality of life of various treatments in acute myeloid leukemia and high-risk myelodysplastic syndrome? Rethinking the goals. American Society of Hematology website. https://ash.confex.com/ash/2015/webprogram/Paper81364.html. Accessed December 18, 2015.

Insurance Status Determines OS in Patients With CML

SURABHI DANGI-GARIMELLA, PHD

Although survival among patients diagnosed with chronic myeloid leukemia (CML) has greatly improved with the advent of tyrosine kinase inhibitors (TKIs), issues with access to care—including medication cost and adherence—can reduce therapeutic efficiency. Ashley M. Perry, from Massachusetts General Hospital in Boston, presented a study that evaluated overall survival (OS) as an outcome of insurance coverage for patients being treated for CML.[1] Perry indicated that approved TKIs in the United States cost anywhere between $92,000 and $138,000 annually and this high cost may influence treatment decisions or result in poor adherence among patients with cancer.

Study results have shown that the uninsured or Medicaid enrollees are highly vulnerable to poor outcomes when diagnosed and treated for cancer. One such study, published in the *Journal of Clinical Oncology*, examined the association of insurance status in patients younger than 64 years who were diagnosed with the 10 most deadly cancers.[2] The uninsured and those on Medicaid presented with more advanced disease, were less likely to receive cancer-directed surgery and/or radiation therapy, and experienced worse survival, the study reported, stressing the importance of insurance coverage in this population of patients.

For their study, Perry and colleagues used the Surveillance, Epidemiology, and End Results Program (SEER) database to perform a population-based analysis to determine if insurance status at the time of CML diagnosis influenced patient outcomes. Patients 15 years or older, diagnosed with CML between 2007 and 2012 and with documented insurance status at diagnosis, were categorized as either private insurance, Medicaid coverage, or uninsured. Patients with unknown insurance status at diagnosis were excluded, as were uninsured patients older than 65 years.

Between 2007 and 2012, 5784 patients were diagnosed with CML and had insurance status documented at diagnosis. A total of 3636 patients were included in the study in the 15-to-64 age group and 2148 in the 65-and-over age group. Of patients aged 15 to 64 years, uninsured and Medicaid patients were younger, more often nonwhite race and Hispanic ethnicity, and less often married, the study results found. Over age 65, Medicaid patients were more often female, nonwhite race and Hispanic ethnicity, and less likely to be married. Additionally, Perry shared that patients in the 15-to-64 age group who were insured were from counties where the unemployment rate was lower, very few people lived below the poverty line, and most people had at least a high school education. The Medicaid population, were mainly from counties with higher education and very few individuals living below the poverty line; however, there was no association observed with unemployment.

With a median follow-up of 32 months, patients in the 15-to-64 age group, who were uninsured or had Medicaid, presented with worse survival compared with insured patients (5-year OS: uninsured, 72.7%; Medicaid, 73.1%; insured, 86.6%; P <.0001). For patients over age 65, the analysis found no difference in 5-year OS between patients with Medicaid and those with other insurance (40.2% vs 43.4%; P = .0802).

In the 15-to-64 age group, compared with insured patients, there was increased mortality among patients who were uninsured (hazard ratio [HR], 2.156; P <.0001) or on Medicaid (HR, 1.972; P <.0001). Additionally, survival was poor with increased age, among males, and among those who were single. For patients over age 65 at diagnosis, age was primarily associated with increased mortality.

Perry concluded that despite highly effective therapies, insurance status can significantly impact outcomes. She noted, however, that the SEER database has certain limitations in terms of the data that is recorded, including the absence of comorbidity data. Despite the availability of highly effective therapies for CML, these findings suggest that many patients may not have access to or receive appropriate care, in part due to their insurance coverage. **EBO**

REFERENCES

1. Perry AM, Zou T, Brunner AM, Neuberg DS, Fathi AT. The impact of insurance status at diagnosis on overall survival in chronic myeloid leukemia: a population-based analysis. American Society of Hematology website. https://ash.confex.com/ash/2015/webprogram/Paper85250.html. Accessed December 18, 2015.
2. Walker GV, Grant SG, Guadagnolo BA, et al. Disparities in stage at diagnosis, treatment, and survival in nonelderly adult patients with cancer according to insurance status. *J Clin Oncol*. 2014;32(28):3118-3125.

Study Shows Academic Hospitals Better at Caring for ALL Patients

SURABHI DANGI-GARIMELLA, PHD

During a health outcomes session on the second day of the American Society of Hematology meeting, Roberto A. Ferro, MD, from the University of Nebraska Medical Center, presented study results that evaluated the difference in overall survival (OS) between patients with acute lymphoblastic leukemia (ALL) treated in academic hospitals (AHs) versus nonacademic hospitals (NAHs).

"Considering the complications associated with ALL, multidisciplinary leukemia teams may be needed to provide optimal management and selection of optimal therapeutic strategy for patient care," Ferro said. Their study was designed to test the hypothesis that AHs are more likely to have such expertise, adequate resources, standard operating policies, and clinical trials, which may influence early mortality and OS in ALL.

To test this hypothesis, the authors used the National Cancer Data Base (NCDB) Participant User File and extracted patient-level data of all patients with ALL reported between 1998 and 2012. Starting with a cohort of more than 20,000 cases, the authors applied certain filtering criteria, such as complete data on variables that included sex, age, education, income, chemotherapy use, 30-day mortality, etc. Patients who received all of their first-course treatment or a decision not to treat made at the reporting facility were included. This narrowed the number of patients in this particular study to 9863.

Ferro said that the hospital facilities were classified as either an AH (academic/research program) or a NAH (community cancer program, comprehensive community cancer program, and other, as per NCDB classification). He explained that per their analysis, 5710 (57.9%) of the 9863 patients with ALL were treated in AHs and that a significantly greater number of patients treated at AHs:

- were African American
- were uninsured or Medicaid enrollees

- had traveled long distances to receive healthcare and a transplant as part of their treatment.

Based on the data shared by Ferro, the median OS (23 vs 17 months) and 1-year OS (67% vs 59%) were better in AH compared with NAH. Further, the 30-day mortality was significantly worse in NAH compared with AH (odds ratio, 1.206; 95% CI, 1.011-1.44; *P* <.0374).

"Our data suggest a need for interventions that can help prevent existing disparity between academic versus non-academic care facilities, at least with respect to care of ALL patients," Ferro said. He suggested that the OS of patients with ALL can be improved by initiating therapy in an AH, which boasts a better provider experience, enhanced multidisciplinary care, and access to clinical trials, among other factors. **EBO**

Healthcare Utilization in Children With Sickle Cell Disease

SURABHI DANGI-GARIMELLA, PHD

Sickle cell disease (SCD) is characterized by marked heterogeneity in clinical outcomes, severity, and utilization of health care services. SCD, a commonly inherited blood disorder resulting from abnormal hemoglobin, is associated with lifelong disabilities and can reduce life expectancy. The disease, which affects between 90,000 and 100,000 people in the United States, is estimated to exceed $1.1 billion annually in medical care costs, alone, for these patients, according to a study published in 2009 in the *American Journal of Hematology*.[1] The heterogeneity of SCD is particularly evident in the utilization of inpatient hospital services, in that some children with SCD are frequently admitted to the hospital, while others are rarely or never admitted, at all. In addition, rates of readmission, within 30 days of hospital discharge, are high in SCD. However, the causes for this variability in utilization and high rates of readmission are not well understood.

To better understand the factors that influence this disparity in outcomes in children with SCD, researchers at the Aflac Cancer and Blood Disorders Center, Emory University School of Medicine, sought to determine rates and primary causes of SCD-related hospital utilization among children and adolescents with SCD. The poster was presented during a Health Services and Outcomes Research session at the annual meeting of the American Society of Hematology.[2]

Children with a confirmed diagnosis of SCD (n = 1331), living in the greater metro Atlanta area, were included in the study. These children had been treated at the Children's Healthcare of Atlanta between January 1, 2010, and December 31, 2014. To ensure a substantial period of observation, individuals with 2 consecutive encounters greater than 18 months apart or with less than 2 years of observation, were excluded. Following a review of the patient's hematologic and clinical data, individuals with rare SCD genotypes were excluded. The primary cause for each admission was determined through medical chart review and classified into 4 mutually exclusive categories: acute chest syndrome (ACS), pain crisis, fever/infection, and other complications of SCD. Scheduled hospitalizations for elective procedures were excluded. A hospitalization occurring within 7, 14, or 30 days of a previous hospital discharge was defined as a readmission.

The study included a nearly equal distribution of male and female patients, with age, at the time of the earliest encounter, ranging from 2 months to 19 years. The children were observed for an average period of 4.02 years. Of the 5317 hospitalizations among the 1331 children, 19.4% were never hospitalized, and 44.8% were hospitalized less than once each year. With the lowest hospitalization rates observed among children between 4 and 9 years of age, overall and cause-specific hospitalization rates varied by age and SCD genotype; pain was the dominating reason for hospitalization (responsible for 53.1% of admissions). Older children with SCD were hospitalized more often for pain-related care, and less often for fever or infection.

Of the 1073 patients who were admitted, the authors found that 356 were readmitted within 30 days of a previous admission at least once. All-cause 7-, 14-, and 30-day readmission rates were 5.6%, 10.0%, and 18.2%, respectively. Thirty-day readmission rates were lower among younger age groups (15.7% for age 1 to 3 years, 15.3% for 4 to 6 years, and 15.8% for 7 to 9 years), but higher in older patients (18.3% for 10 to 12 years, 19.9% for 13 to 15 years, and 23.3% for 16 to 18 years). Readmission rates were highest for pain (20.4%) and lowest for ACS (11.3%), independent of gender, and 34% of all 30-day readmissions occurred during the first week of discharge.

These results led the authors to the following conclusions:

- SCD-related hospitalization rates were highest in early life and in later adolescence.
- Admissions for fever or infection were most common in younger children, and admissions for pain crises in older children.
- Rates of readmission strongly correlated with age, and were highest following admissions for pain.
- The risk of 30-day readmission is highest in the first 7 days following discharge in this study population. **EBO**

REFERENCES

1. Dangi-Garimella S. Care plans to reduce healthcare utilization in sickle cell disease. *Am J Manag Care*. 2015;21(SP1):SP8-SP9.
2. Theodore R, Barry V, Quarmyne M, Dampier C, Lane PA. Inpatient utilization among children and adolescents with sickle cell disease: analysis of a large populated-based retrospective cohort. American Society of Hematology website. https://ash.confex.com/ash/2015/webprogram/Paper86574.html. Accessed December 20, 2015.

Does Geographic Location Influence Healthcare Utilization in Children With Lymphoma?

SURABHI DANGI-GARIMELLA, PHD

Geographic location can prove to be an important, and sometimes, life-threatening barrier to healthcare access, especially for a complicated disease like cancer. In these cases, the most advanced care services may be offered only by select hospitals or clinics in metropolitan regions.

To assess healthcare utilization and costs in children with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) based on geographic distance from their primary cancer center, researchers at the Children's Mercy Hospital in Kansas City, MO, analyzed data from the Pediatric Health Information System (PHIS) database, which collects information for inpatient resource utilization at 48 children's hospitals in the USA. The premise of the study, which was presented at a Health Services and Outcomes Research session at the annual meeting of the American Society of Hematology, was that distance from the site of care can delay access to care services, resulting in complications that can increase healthcare costs.

The authors analyzed data from patients (21 years or younger) who were diagnosed with ALL or AML between the first quarter of 2010 and the third quarter of 2013. The total number of hospitalizations and resources utilized and billed were measured 12 months following the index hospital stay for ALL patients, and 6 months for AML patients. Data gathered from PHIS included total cost per day, length of stay (LOS), prevalence of ICU stay, prevalence of total parental nutrition (TPN) use, and ventilator use. Stratified data, depending on chemotherapy vs non-chemotherapy stays, were compared between children living less than 60 miles versus more than 60 miles from the PHIS hospital.

For the ALL group, 12,884 hospital admissions were recorded for chemotherapy and 13,842 admissions for non-chemotherapy. Based on their analysis, the authors concluded that travel distance to the hospital (less than or more than 60 miles) did not impact ICU, TPN, or ventilator days among patients admitted for chemotherapy. However, there was significantly greater ICU stay (4.5% vs 6.1%, $P = .001$) and TPN use (5.1% vs 6.6%, $P = .004$) in children living more than 60 miles from the hospital who were admitted for non-chemotherapy purposes.

In children with AML, 2855 chemotherapy and 1414 non-chemotherapy–related admissions were recorded. In this cohort, the results were different than those observed with the ALL patients. AML patients living more than 60 miles away from the hospital and admitted for chemotherapy had longer LOS, and more ICU use (4.1% vs 6.7%, $P = .009$). Those admitted for non-chemotherapy purposes who lived beyond 60 miles of the hospital had more prevalent ICU (8.3% vs 14.5%, $P = .03$) and TPN use (9.7% vs 15.7%, $P = .06$), and greater hospitalization cost and cost per day.

The results of the study support the hypothesis that geographic distance from cancer centers increases healthcare resource consumption and cost, at least for unplanned admissions associated with complications in children with ALL and AML. This, in turn, implies that distance from the site of care could result in adverse complications in these critically ill children and could adversely affect outcomes. **EBO**

REFERENCE

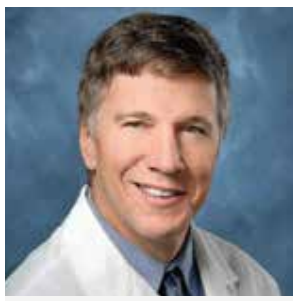
Hall NS, Gamis AS, Hall M. Comparing the utilization of health care resources in children with ALL and AML based on geographic location: a retrospective analysis utilizing the PHIS database. American Society of Hematology website. https://ash.confex.com/ash/2015/webprogram/Paper79149.html. Accessed December 20, 2015.

Do Hematologists Believe APMs Afford Fair Value? An Open Discussion at ASH

SURABHI DANGI-GARIMELLA, PHD

Alternate payment models, bundled payments, risk sharing, value-based payments—discussions around these new payment models have found a permanent place in clinical oncology meetings. Initially developed for primary care or common surgical procedures, payment models are also being developed for patients with hematologic diseases. On the second day of the annual meeting of the American Society of Hematology (ASH), physicians gathered to discuss the impact of alternate payment models—proposed by CMS and by private health plans—on clinical practice.

Moderator Steven L. Allen, MD, from the North Shore-Long Island Jewish Health System, Manhasset and New Hyde Park, NY, and chair of the ASH Committee on Practice, said, "Physicians need to be aware of how insurers pay for their services, even if their income is entirely based on salary. Our speakers will address bundled payments, using hematopoietic stem cell transplantation as the model, followed by a review of resource management, since controlling costs is crucial in all payment models. Finally, we will hear from an insurer who will discuss what is happening in this new environment and how insurers plan to handle the transfer of risk from the insurer to the provider."



MICHAEL LILL, MD

Using hematopoietic cell transplantation (HCT) as a model, Michael Lill, MD, from Cedars-Sinai Medical Center, Los Angeles, said that HCT is a high-cost, high-risk, and high-benefit procedure, with high resource utilization—but patients can be cured. He listed several barriers for entry of institutions into HCT:

- Shortage of trained physicians
- Need for accreditation
- Restrictions rendered by insurance companies, such as the need to be a center of excellence and the need for outcomes data
- Substantial infrastructure needs

Providing a historical context to the evolution of payment models in HCT, Lill explained that payment models for HCT were initiated in the 1990s, but the incentives were poorly aligned, with a 100% risk on the payer. "So the concept of bundled payment came about to share the risk between payers and providers and to incentivize providers to be more efficient," Lill said. Bundled payment continued to leave HCT as a profit center at most hospitals and "it helped center directors focus their attention on costs of care," he explained.

Explaining the nuances of an HCT bundled payment, Lill explained that a transplant episode is divided into the following phases: assessment, donor identification, conditioning therapy administration and other supportive care, and post-discharge follow-up. The nature of bundles varies from one contract to the next, and each phase of the bundle described above involves a technical fee (which goes to the institution) and a professional fee (which goes to the physician). The professional fee is very minor, usually 5% to 10% of the cost of care of HCT.

"The professional fee can be quite straightforward if it is not included in the bundle," explained Lill. "However, inclusion in the bundle makes things complicated. What do providers bill the overall bundle? Should they charge the Medicare rate or the PPO rate or the cash pay rate?" These complications create a need for negotiation and then a separate contractual arrangement with the private practice providers, he said.

In addition, long-term management and payment problems emerge for patients who might see a different provider 6 months following their transplant, but who are still on the case rate. Providing an example of a transplant patient who might come down with pneumonia and seek care at a local emergency department, Lill said, "We need clear definitions of what is and what is not covered in the bundle."

Provisions such as stop-loss payments further the complication. "A typical global contract will specify payments for a well-defined episode of care, specify a rate that will start after the contract episode ends," Lill said, explaining that stop-loss payments help ensure that the hospital or institution does not shoulder the entire risk. The stop-loss clause, he said, states that once a certain threshold in charges is reached, the payer will pay a percentage of charges for a particular episode of care.

JOSEPH ALVARNAS, MD

Outlining the pros and cons of bundled payments, Lill listed the following advantages of a bundled payment model:

- Physician control over patient care plan
- Absence of pre-authorization requirements
- Close attention to expenditures and outcomes by those in the know
- Incentive for innovation
- More predictable cost structures for insurers

The disadvantages include:

- Being in control, the physician is responsible for decisions made, not the payer (especially relevant when holding back care)
- Treatment strategies include cost-benefit-profit analyses
- Physicians out of tune with the business of medicine
- Physicians may not be comfortable with these concepts
- Potential for conflicts of interest

"We have had 25 years of experience with this payment model in the transplant field," said Lill, emphasizing that although cost decisions are made explicit to providers, we need to ensure that providers are not inappropriately influenced by the payment model. "Outcomes data become very important with bundles, and they can also lead to innovations in clinical practice," he said.

The next presentation by Joseph Alvarnas, MD, Hematology/HCT, City of Hope National Medical Center in Monrovia, California, was titled, "Measuring Episodes of Care and How to Turn Them into Payment." Alvarnas, the editor in chief of *Evidence-Based Oncology*, posed the question, "Is episode of care more a modality-driven care in patient's care?"

Emphasizing the influence of the Affordable Care Act on changes in healthcare payments and infrastructure, Alvarnas said that non–fee-for-service payment models are shifting the ownership of the entire care continuum onto providers. "Providers are now responsible for direct care costs, readmissions, and complications of treatment," he said. Although this concept creates negative incentives for ineffective, expensive, or duplicate treatments, it simultaneously shifts the risk onto consumers through higher deductibles, copays, co-insurance payments, and out-of-pocket expenses, Alvarnas clarified. For diseases like acute leukemia, increased risk-sharing funds the alignment between knowledge, risk, and reimbursement, he said.

Cancer care costs are rising rapidly, specifically for acute leukemia, which represents 1.7% of all new cancer diagnoses. Studies have shown that it accounts for $5.4 billion in cancer care costs. "But do we really know how much it costs to treat someone with acute leukemia?" Alvarnas asked the audience. A lot of these figures, he said, are derived from international trials; estimated costs do not consider the high interpatient variability associated with this disease. "Further compounding

(continued on **SP30**)

imbruvica®
(ibrutinib) 140mg capsules

DISCOVERING HOW FAR THERAPY CAN GO

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

IMBRUVICA® is approved for use in 4 indications

IMBRUVICA® is indicated for the treatment of patients with

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

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

Chronic lymphocytic leukemia with 17p deletion.

Waldenström's macroglobulinemia (WM).

ADVERSE REACTIONS

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

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

†Includes multiple ADR terms.

‡Not applicable; no associated ADRs.

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

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

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

DRUG INTERACTIONS

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

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

SPECIFIC POPULATIONS

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

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

To learn more, visit
www.IMBRUVICA.com

06/15 PRC-01166

pharmacyclics®
An AbbVie Company

janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

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

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

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

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

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood.

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

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

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

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

Monitor complete blood counts monthly.

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

* Based on laboratory measurements and adverse reactions

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

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

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

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

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

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

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

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

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

**One patient death due to histiocytic sarcoma.*

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

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

* Based on laboratory measurements per IWCLL criteria and adverse reactions

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

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

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

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

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

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

* Based on laboratory measurements per IWCLL criteria

Waldenström's Macroglobulinemia

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

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

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

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

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

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

IMBRUVICA® (ibrutinib) capsules

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

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

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

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

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

* Based on laboratory measurements.

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

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

DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

Risk Summary: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

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

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

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

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

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

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

(continued from **SP25**)

the complexity is the fact that none of these data are linked to meaningful outcomes. For the cost to be meaningful, it should be linked to how it affects the patient," Alvarnas stressed.


MICHAEL KOLODZIEJ, MD

He asked: how can we come up with a payment model that can encompass all of the factors associated with disease treatment modalities, such as patient age, demographics, disease status risk, cytogenetic and molecular risks, and treatment modality–related financial risk? Citing CMS' episode-of-care payment model, he said that the model defines an episode as 6 months of care, with the clock set in motion with a new disease diagnosis, relapse, or disease progression.

"While the sensibilities behind the episode-of-care payment model are right—namely providing longitudinal care and creating economic incentives for data-driven care delivery—it is unclear if this model is suitable for acute leukemia," Alvarnas declared, suggesting that the shared-savings model might be a better approach. As we move toward value-based care, we need cost-insensitive care delivery, with an emphasis on achieving systemness in care, he said.

The final presenter was Michael Kolodziej, MD, national medical director for Oncology Solutions at Aetna. He provided insight into the payer approach to new cancer payment methods. Kolodziej emphasized that patients with cancer do care about the quality of care they receive, and providers and payers should be wary of that.

"The major healthcare challenges today are a rapidly-aging population and the growing expense of healthcare, a lot of which is contributed by high drug prices," said Kolodziej. However, it's not just the sticker price of the drugs, in his opinion, that's responsible for escalating costs. Cancer is the most costly medical item, he said—not just drugs, but the overall care of cancer patients is expensive.

What most health plans care about, Kolodziej said, is end-of-life use of medical services. He shared statistics showing that one-third of patients are in the intensive care unit in the last month of their life—something that he said was quite unusual a few years back while he was still a practicing oncologist.

He listed a few strategies used by health plans to combat the rising cost of cancer care:

- Pay less
- Manage more (prior authorization)
- Narrow networks
- Increase co-payments
- Incorporate process measures and link them to outcomes (pay-for-performance)
- Shift risk (capitation)

Kolodziej emphasized that generating value is THE solution in oncology. "We can provide quality care and optimize the right treatment to the right patient at the right time according to the patient's needs," he said. Additionally, adherence to evidence-based guidelines decreases cost without a negative impact on outcomes.

Using well-validated clinical pathways also helps provide structure and contain costs, he said, but pathways are just a part of the process measures. "Medical homes are also a part of the solution," according to Kolodziej, and he believes the Oncology Care Model developed by the Center for Medicare and Medicaid Innovation, can draw parallels to the Oncology Medical Home (OMH). "And OMH is an ACO solution."

> **"Although [a non–fee-for-service model] creates negative incentives for ineffective, expensive, or duplicate treatments, it simultaneously shifts the risk onto consumers through higher deductibles, copays, co-insurance payments, and out-of-pocket expenses. For diseases like acute leukemia, increased risk-sharing funds the alignment between knowledge, risk, and reimbursement."**
>
> –JOSEPH ALVARNAS, MD

Performance on process measures and outcomes measures can have a significant impact on pathways, explained Kolodziej. "Ultimately, pathways are just a scaffolding that help structure and manage patient care. We have to remember that you cannot improve data that you do not measure," he concluded. **EBO**

THE AMERICAN JOURNAL OF MANAGED CARE®

CALL FOR PAPERS

HCV Special Issue

The American Journal of Managed Care (*AJMC*) is issuing a call for papers for a special issue on the hepatitis C virus (HCV), set to be published in March 2016. This issue will feature scholarly articles and perspectives from a range of stakeholders and researchers, with the goal of defining the impact, innovations, and challenges related to HCV.

We are seeking a limited quantity of original research papers and informed commentary on HCV-focused topics in the following areas:

- New innovations for interventions and the diagnosis and treatment of HCV
- Post-marketing outcomes for new agents in HCV
- The evolving role of quality measures for management of HCV
- Effects of healthcare reform on HCV care
- Challenges and best practices in providing access to the entire continuum of care
- Impact of plan design on patient access to appropriate therapies
- Barriers to patient adherence
- Improving coordination of care
- Methodologies for provider and payer accountability
- Innovative partnerships between payers, providers, and manufacturers
- Effects of changing capitation and reimbursement on healthcare delivery
- Cost of new therapeutic agents and their impact on utilization
- Balancing cost silos—medical versus pharmacy spend
- Best practices in cost sharing
- Comparative effectiveness research and methodologies
- Examples of integrating evidence-based guidelines into practice
- Implications of HCV coverage decisions for other disease areas and patient populations

Due to space constraints, we request that you limit your manuscript's text to 2500 words or less (excluding references) and its graphic elements to 3 figures and/or tables total. The final decision regarding a paper's acceptance will be made by the editors; each accepted paper will be peer-reviewed. High-quality papers not selected for publication in the special issue will be considered for one of the regular monthly issues of *AJMC*.

Please submit all manuscripts through *AJMC*'s online submission system at **http://mc.manuscriptcentral.com/ajmc** using the category "**Special Issue**."

If you have questions or wish to speak to an editor, please e-mail: **nbeagin@ajmc.com**

Using Technology to Bring Palliative Care to the Patient's Doorstep

SURABHI DANGI-GARIMELLA, PHD

There is no arguing that burgeoning healthcare costs are a major concern for the economy, and value-based models are carving out paths to reduce healthcare utilization without compromising on the quality of care for the patient. A review of Medicare payments in the last year of life found that over an 8-year period from 1978 to 2006, Medicare expenditures of beneficiaries in their last year remained nearly steady at over 25%.[1] This is where end-of-life (EOL) discussions would matter. Initiating a conversation on care plans at EOL with patients and their families have been documented to create a fair balance—improving the quality of life for patients during the last few weeks of life and lowering healthcare utilization.[2]


MARK GANZ

Evidence points to palliative care as an answer to improving the patient quality of care while reducing costs. However, several barriers exist with access to palliative care, including a shortage of trained specialists, insufficient training of care providers, and lack of knowledge or misconceptions among patients and their families as well as care providers. Having realized the advantages of integrating palliative care in mainstream patient care, insurers like Cambia Health Solutions have been proactively working to improve patient access to palliative care.

Cambia's program, launched over a year ago in July 2014, offers reimbursement for services that include advance care planning, care coordination, and medical team conferences among care providers of seriously ill patients. Additional covered services under the program include reimbursement for home aides, in-home counseling, and provider training to engage patients and their families in EOL care planning.[3]

Mark Ganz, president and CEO of Cambia believes, "If we engage palliative care early enough, then actually patient outcomes are far better."[4] Ganz has a personal story to narrate, which has fed his passion to promote palliative care. His mother's care providers ignored her wish of "do not resuscitate" the night she died. Pointing to a healthcare system that is extremely well-adapted to a fee-for-service model that pays more for the amount of care a hospital provides its patients, Ganz says, "It reflects a culture in healthcare that's very much locked into the economic model."

To expand the reach of palliative care beyond the clinic and to develop tools that can improve patient access to this care service, Cambia is reaching out to technology innovators by participating in meetings like Health 2.0. By developing apps and tools to help patients make EOL choices or receive palliative care in the comfort of their home. The company's belief in this process is evident in the fact that Cambia employees are themselves offered the option of advance care planning. **EBO**

REFERENCES

1. Riley GF and Lubitz JD. Long-term trends in Medicare payments in the last year of life. *Health Serv Res*. 2010;45(2):565-576.

2. Zhang B, Wright AA, Huskamp HA, et al. Health care costs in the last week of life: associations with end of life conversations. *Arch Intern Med*. 2009;169(5):480-488.

3. Johnson SR. Palliative care medical home pilot starting in the West. Modern Healthcare website. http://www.modernhealthcare.com/article/20140620/NEWS/306209959. Published June 20, 2014. Accessed December 30, 2015.

4. Kutscher B. Cambia Health invites tech innovators to help change palliative care. Modern Healthcare website. http://www.modernhealthcare.com/article/20151227/NEWS/151229953?utm_source=modernhealthcare&utm_medium=email&utm_content=20151227-NEWS-151229953&utm_campaign=dose. Published and accessed December 27, 2015.

Improving Cancer Trial Participation via Web-Based Interventions

SURABHI DANGI-GARIMELLA, PHD

Patient awareness and educational support can improve their attitude, as well as prepare them to make better informed decisions on clinical trial participation, a new study has found.

Published in the *Journal of Clinical Oncology*,[1] the study, led by Neal Meropol, MD, of the Case Western Reserve University School of Medicine, was a collaboration across 5 cancer centers, including the Robert Lurie Comprehensive Cancer Center at Northwestern University, Cleveland Clinic Foundation, Fox Chase Cancer Center, and Karmanos Cancer Institute at Wayne State University. Identifying knowledge gaps as one of the barriers of low clinical trial participation by cancer patients, the researchers developed an educational tool called the Preparatory Education About Clinical Trials (PRE-ACT), a Web-based computer program that delivers tailored video educational content to patients so they give serious consideration to clinical trials as a treatment option.


NEAL MEROPOL, MD

After randomly sorting 1255 cancer patients into a PRE-ACT (623) or control (632) group prior to their visit with an oncologist, the authors found that 21% of patients chose to participate in clinical trials, which is a big contrast to the traditional number of less than 5% trial participants. The control group was exposed to general information on clinical trials developed by the National Cancer Institute. Said Meropol, "Unfortunately, although clinical trials are critical for advancing cancer treatment and ultimately serve as the basis for new standards of care, very few patients participate. We want to close the patient knowledge gap and positively affect their attitudes toward clinical trials."[2]

PRE-ACT had 3 components:

- Assessment of clinical trials knowledge and attitudinal barriers
- Values assessment with clarification back to patients
- Provision of a video library tailored to address each patient's barriers

The outcomes evaluated were knowledge and attitude and preparation for decision making about clinical trials. While the authors observed significant improvement in knowledge and attitudes in both groups following PRE-ACT and control interventions, patients in the PRE-ACT group—exposed to educational video programs—had significantly greater increase in knowledge and a decrease in attitudinal barriers compared with patients in the control group. While participants in both groups were more eager to participate in clinical trials, there was a non-significant trend for increased participation in the PRE-ACT group.

"By identifying knowledge gaps and negative attitudes and addressing those before patients meet their doctors to discuss cancer treatment, the patient will be better prepared to make a good decision about whether a clinical trial will be an appropriate option for them. We hope PREACT will result in increased participation in clinical trials by cancer patients through improving knowledge and attitudes and facilitating treatment decision-making," said Meropol. **EBO**

REFERENCES

1. Meropol NJ, Wong Y, Albrecht T, et al. Randomized trial of a Web-based intervention to address barriers to clinical trials. *J Clin Oncol*. 2015. pii: JCO632257.

2. Educating patients about cancer treatment clinical trials improves knowledge and attitudes about participating in research. newswise website. http://www.newswise.com/articles/view/645304/?sc=dwhr&xy=10014716. Published December 23, 2015. Accessed December 28, 2015. 03-1813.

Cancer's Toll Beyond the Disease: *Medical Costs and Productivity*

SURABHI DANGI-GARIMELLA, PHD

With nearly 18 million estimated survivors by 2022,[1] cancer care in the United States needs a coordinated agenda to be successfully able to address the long-term medical as well as economic needs of survivors. Highlighting the economic burden on survivors is a new report from the American Cancer Society, published in the *Journal of the National Cancer Institute*, which found that younger colorectal cancer survivors end up spending over $8500 annually in medical expenses and they also experience significantly greater loss of productivity compared with individuals without cancer.[2]

Evaluating the impact of medical costs on survivors of 3 cancers: colorectal, female breast, and prostate, researchers from the American Cancer Society segregated the elderly and the younger population of survivors. Using data gathered by the Medical Expenditure Panel Survey[3]—a national data source that measures use and costs of medical care, health insurance, and out-of-pocket spending in the United States—between 2008 and 2012, the study included 540 colorectal cancer survivors, 1568 female breast cancer survivors, 1170 prostate cancer survivors, and 109,423 individuals without cancer. They compared the excess economic pressures that survivors experienced due to their disease, as well as loss of productivity associated with taking time off from work.

Young cancer survivors included in the study witnessed a significant impact of cancer on their annual medical expenses, as well as on their productivity at work. Those who survived colorectal cancer had an average excess of $8647 in medical costs; breast cancer survivors, $5119; and prostate cancer survivors, $3586. Costs were relatively lower for the elderly survivors, but greater nonetheless than the comparator population: $4913 for colorectal, $2288 for breast, and $3524 for prostate.

Younger survivors of colorectal and breast cancer had significantly greater employment disability (13.6% and 4.8%, respectively) compared with those without cancer. They also lost more work days: 7.2 days on average for colorectal cancer survivors and 3.3 days for breast cancer survivors. Surprisingly, the elderly population included in the study had comparable productivity losses as those without a history of cancer in their age group.

These results indicate that survivors continue to experience disease-related symptoms even after being declared disease-free, but are forced to get back to work, likely due to monetary needs and to maintain health insurance coverage. A National Cancer Institute–funded study at the Massey Cancer Center at Virginia Commonwealth University has been investigating the impact of provisions within the Affordable Care Act (ACA) that can help individuals who depend on employer-sponsored health insurance.[4] Preliminary results have indicated that with the ACA, cancer patients will not have to worry about loss of insurance coverage if they can no longer work. This would allow survivors to focus on their path to recovery and improve their quality of life. **EBO**

REFERENCES

1. de Moor JS, Mariotto AB, Parry C, et al. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. *Cancer Epidemiol Biomarkers Prev.* 2013;22(4):561-570.

2. Zhiyuan Zheng, K. Robin Yabroff, Gery P. Guy, et al. Annual medical expenditure and productivity loss among colorectal, female breast, and prostate cancer survivors in the United States. *J Natl Cancer Inst.* 2015;108(5). pii: djv382.

3. Medical Expenditure Panel Survey (MEPS). Agency for Healthcare Research and Quality website. http://www.ahrq.gov/research/data/meps/index.html. Accessed December 28, 2015.

4. Researchers examine effects of ACA on cancer survivors. News Medical website. http://www.news-medical.net/news/20140124/Researchers-examine-effects-of-ACA-on-cancer-survivors.aspx. Published January 24, 2014. Accessed December 28, 2015.

Progress Toward Healthy People 2020: *CDC Report Claims Reduction in Cancer Incidence*

SURABHI DANGI-GARIMELLA, PHD

Launched in December 2010, Healthy People 2020 has an agenda to achieve significant improvement in the health of the population in America by 2020, with disease-specific milestones established along the path. The project aims to reduce the number of new cancer cases, illness, disability, and death from cancer.

As a part of this overall objective, CDC analyzes data across the country, comparing cancer incidence and survival rates and reporting them to the public. The latest report has released analysis of data from the U.S. Cancer Statistics (USCS) for 2012, which is the most recent data available. USCS includes high quality incidence data from CDC's National Program of Cancer Registries (NPCR) and the National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER), survival data from NPCR, and mortality data from the National Vital Statistics System.

Here are the key findings of the report:

- A total of 1,529,078 new cases of invasive cancers were diagnosed in the United States in 2012.
- Highest incidence was in those 75 years and older, which corroborates the association of cancer and ageing.
- Annual incidence rate was 483 per 100,000 among men and 412 per 100,000 among women.
- All-sites cancer ranged between 371 and 515 per 100,000 persons.
  - Puerto Rico had the lowest incidence rates for all sites compared with Washington DC and the 50 states. Additionally, Puerto Rico also had the lowest incidence for lung cancer and female breast cancer.
- As has been reported in individual studies, prostate cancer incidence did see a reduction in 2012 compared with 2011.
- Thirty states achieved the Healthy People 2020 targets for reducing incidence rates for colorectal cancer, and 27 states met the target for cervical cancer.
- Overall, more than 65% of those diagnosed with cancer survived 5 years or longer following their diagnosis between 2001 and 2011.
  - The younger population (less than 45 years) performed much better with 5-year survival than the older population, irrespective of gender or race.
  - Highest rates for 5-year survival were achieved for prostate cancer (97%) and female breast cancer (88%).
  - A gender bias was observed—the 5-year survival after any cancer diagnosis was lower for blacks (60%) than for whites (66%), and more so for black females (57% compared with 66%).
- Based on data from SEER and NPCR, in 2012, cancer incidence was higher in states in the eastern United States compared to the rest of the nations.

The authors attribute the decrease in prostate cancer incidence to the recommendation by the US Preventive Service's Task Force (USPSTF) against using the prostate-specific antigen (PSA) test for screening men for prostate cancer. Studies recorded an 8% reduction in the use of the PSA test following the USPSTF recommendation: from 32% in 2008 to 24% in 2013.

The authors urge the population—and particularly, the healthcare providers—to follow the new screening recommendations by USPSTF for the various cancers to be able to achieve improved cancer outcomes in the population. Maximizing efforts to prevent cancer, improve adherence to cancer screening recommendations, and assure timely and appropriate cancer care for all persons is needed to achieve the national cancer objectives set forth in Healthy People 2020, they write. **EBO**

REFERENCE

Henley SJ, Singh SD, King J, et al. Invasive cancer incidence and survival–United States, 2012. CDC website. http://www.cdc.gov/mmwr/pdf/wk/mm6449.pdf.

NOW APPROVED

DARZALEX™
(daratumumab)
injection for intravenous infusion
100 mg/5 mL, 400 mg/20 mL

Please visit
www.darzalex.com

 11/15 035821-150617

Janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson