Bridging the gap between payer and provider perspectives

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Evidence-Based Oncology

Payment Reform

Is Medicare Ready for Oncology Clinical Pathways?

Stanton R. Mehr

Medical costs associated with cancer have increased dramatically, and they are projected to rise much further—to more than $173 billion per year by 2020.[1] Many factors are responsible for this rapid rise: greater use of specialty drugs, more patients with cancer as the population ages, and more costly care environments, as more cancer care moves out of community settings and into hospitals.[2] Another challenging factor—the variability in costs of care as well as practice—is being addressed through the evolution of oncology practice guidelines into oncology clinical pathways.

The wide variation in treatment patterns and costs among oncologists has been long documented and is apparent in many cancer types.[3–5] In the treatment of thyroid cancer, for example, Haymart and colleagues[5] found significant variation in multiple aspects of management, in central lymph node dissections, in pre-treatment scans before radioactive iodine treatment, and in all aspects of long-term thyroid cancer management. This included different applications of ultrasound and radioactive iodine scans. Another group of researchers found high variation among physicians in basic items, such as how often surveillance occurred after initial therapy in breast cancer.[6]

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Quality Care

Defining, Measuring, and Paying for the Work of Oncology Patient Navigators

Peter Page

Rose Gerber

As cancer increasingly becomes a disease of survivors, oncology sees a need for navigators to help patients identify and pay for appropriate treatment. Navigators also help patients deal with the often overwhelming pressures of maintaining a normal life while managing a potentially fatal disease. So far, however, there is little agreement on how narrow or broad a patient advocate or navigator's work should be—or how to measure the results.[1]

While the idea of a patient navigator is at least 2 decades old,[1] the role has garnered more attention since the 2005 Institute of Medicine (IOM) report, "From Cancer Patient to Cancer Survivor: Lost in Transition,"[2] which detailed the myriad new challenges to providing quality care to patients who are living longer.

Patient navigators are often oncology social workers; some have special training in helping cancer patients from medically underserved populations overcome barriers to appropriate care. Studies of Latino patients suffering from breast and colon cancer found "The presence of patient navigation can be an effective means to re-

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Status in the States

In Cancer and Beyond, Washington State Making the Transition to Value-Based Care

Mary K. Caffrey

Few places put as much emphasis on value-based healthcare as Washington state does. From a governor whose workplace wellness program for state employees requires progress reports every 6 months,[1] to the Health Care Authority's quest for $51 million from the federal government to revamp Medicaid delivery,[2] words like "prevention" and "outcomes" populate every message.

Healthcare reform, as envisioned by the 2010 Affordable Care Act, was a process both the former and current governors fully embraced. Like his counterpart in Kentucky, Washington Governor Jay Inslee presents the expansion of coverage as both a moral imperative and competitive necessity; he says the ACA rollout "has presented us with the ideal opportunity to implement the kinds of cost-saving, health-improving reforms that will help us achieve those goals."[3]

Governor Jay Inslee

In the realm of cancer care, Washington state's relative success in adding nearly 250,000 to the ranks of the insured by January 1, 2014,[4] including 121,258 adults previously not eligible for Medicaid,[4] would seem to put the state on a course of continuing its better-than-typical response to the disease. Washington's early enrollment numbers, along with the governance and performance of its exchange, have

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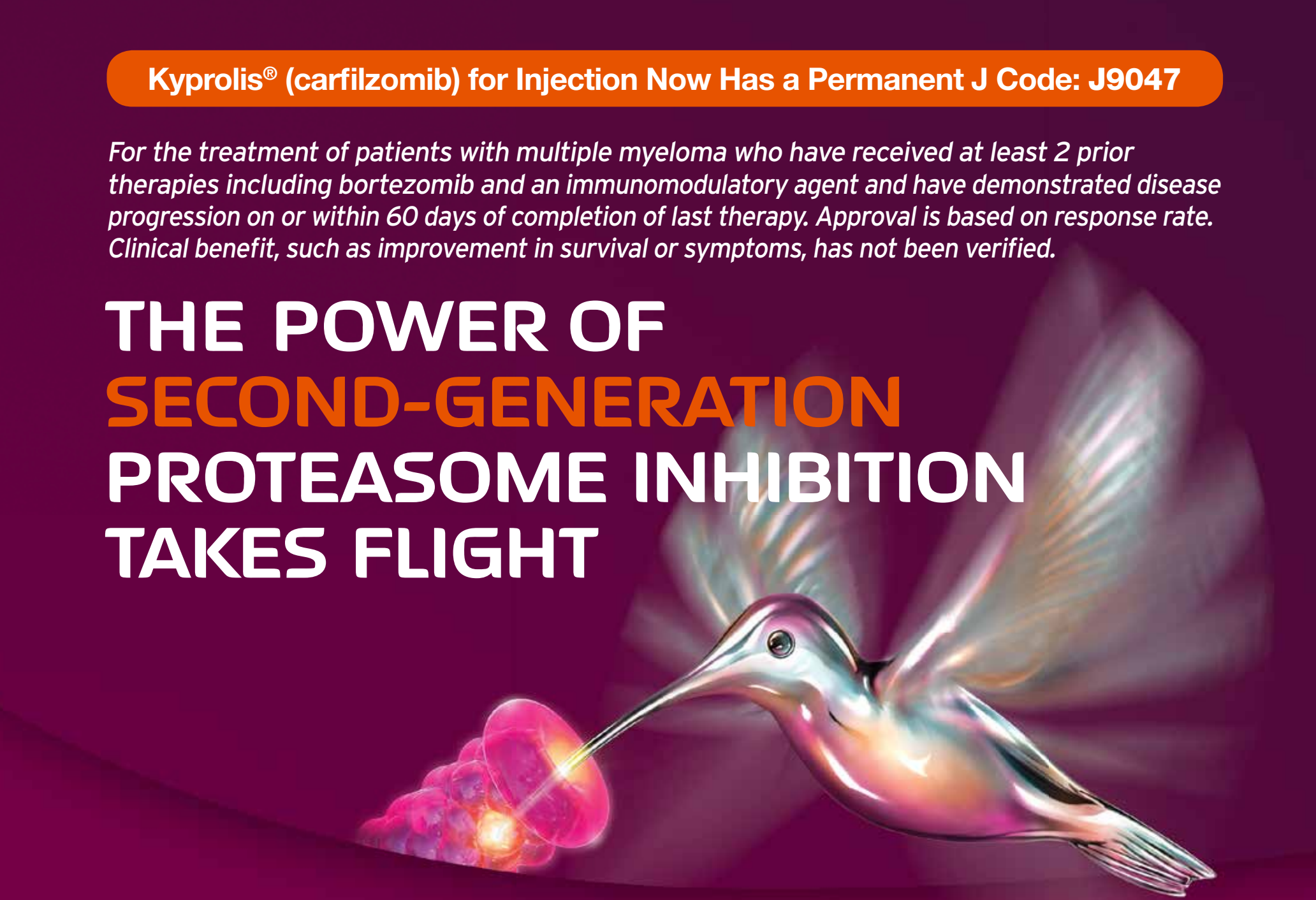
In this issue...

US Rep. Paul Ryan, R-MN, left, and US Sen. Patty Murray, D-WA, announce the budget deal.

Kyprolis® (carfilzomib) for Injection Now Has a Permanent J Code: J9047

For the treatment of patients with multiple myeloma who have received at least 2 prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

THE POWER OF SECOND-GENERATION PROTEASOME INHIBITION TAKES FLIGHT



Important Safety Information

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

The safety of KYPROLIS was evaluated in clinical studies of 526 patients with relapsed and/or refractory multiple myeloma.

Cardiac Arrest, Congestive Heart Failure, Myocardial Ischemia: Death due to cardiac arrest has occurred within a day of KYPROLIS administration. New onset or worsening of pre-existing congestive heart failure with decreased left ventricular function or myocardial ischemia have occurred following administration of KYPROLIS. Cardiac failure events (e.g., cardiac failure congestive, pulmonary edema, ejection fraction decreased) were reported in 7% of patients. Monitor for cardiac complications and manage promptly. Withhold KYPROLIS for Grade 3 or 4 cardiac events until recovery and consider whether to restart KYPROLIS based on a benefit/risk assessment. Patients with New York Heart Association Class III and IV heart failure, myocardial infarction in the preceding 6 months, and conduction abnormalities uncontrolled by medications may be at greater risk for cardiac complications.

Pulmonary Hypertension: Pulmonary arterial hypertension (PAH) was reported in 2% of patients treated with KYPROLIS and was Grade 3 or greater in less than 1% of patients. Evaluate with cardiac imaging and/or other tests as indicated. Withhold KYPROLIS for pulmonary hypertension until resolved or returned to baseline and consider whether to restart KYPROLIS based on a benefit/risk assessment.

Pulmonary Complications: Dyspnea was reported in 35% of patients enrolled in clinical trials. Grade 3 dyspnea occurred in 5%; no Grade 4 events, and 1 death (Grade 5) was reported. Monitor and manage dyspnea immediately; interrupt KYPROLIS until symptoms have resolved or returned to baseline.

Infusion Reactions: Infusion reactions were characterized by a spectrum of systemic symptoms including fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following infusion or up to 24 hours after administration of KYPROLIS. Administer dexamethasone prior to KYPROLIS to reduce the incidence and severity of reactions. Inform patients of the risk and symptoms, and to contact physician if symptoms of an infusion reaction occur.

Tumor Lysis Syndrome: Tumor lysis syndrome (TLS) occurred following KYPROLIS administration in < 1% of patients. Patients with multiple myeloma and a high tumor burden should be considered to be at greater risk for TLS. Prior to receiving KYPROLIS, ensure that patients are well hydrated. Monitor for evidence of TLS during treatment, and manage promptly. Interrupt KYPROLIS until TLS is resolved.

KYPROLIS is engineered for selective inhibition[1]

- Single-agent KYPROLIS phase 2 study results[2,*]
  - Overall response rate (ORR) of 22.9% in PX-171-003 study (95% CI: 18.0, 28.5)
  - Median duration of response of 7.8 months (95% CI: 5.6, 9.2)
- Most patients across all phase 2 studies (85%) did not need to discontinue therapy due to an adverse event
  - Adverse reactions leading to discontinuation included congestive heart failure (2%), cardiac arrest, dyspnea, increased blood creatinine, and acute renal failure (1% each)

ADVERSE REACTIONS

The safety of KYPROLIS was evaluated in clinical trials of 526 patients with relapsed and/or refractory multiple myeloma.

- Serious adverse reactions were reported in 45% of patients. The most common were pneumonia (10%), acute renal failure (4%), pyrexia (3%), and congestive heart failure (3%)
- The most common adverse reactions (incidence ≥ 30%) were fatigue (56%), anemia (47%), nausea (45%), thrombocytopenia (36%), dyspnea (35%), diarrhea (33%), and pyrexia (30%)

*Study PX-171-003 was a single-arm, multicenter clinical trial of KYPROLIS in 266 patients with relapsed multiple myeloma and whose disease had a ≤ 25% response to the most recent therapy or had disease progression during or within 60 days of the most recent therapy. At the time of study entry, patients had received a median of 5 prior lines of therapy. The primary endpoint was ORR. Response was determined by Independent Review Committee assessment using International Myeloma Working Group criteria.

References: 1. Demo SD, Kirk CJ, Aujay MA, et al. Antitumor activity of PR-171, a novel irreversible inhibitor of the proteasome. *Cancer Res*. 2007;67(13):6383-6391. **2.** KYPROLIS [prescribing information]. South San Francisco, CA: Onyx Pharmaceuticals, Inc.; 2012.

Kyprolis™ (carfilzomib) for Injection

Thrombocytopenia: KYPROLIS causes thrombocytopenia with platelet nadirs occurring around Day 8 of each 28-day cycle and recovery to baseline by the start of the next 28-day cycle. In patients with multiple myeloma, 36% of patients experienced thrombocytopenia, including Grade 4 in 10%. Thrombocytopenia following KYPROLIS administration resulted in a dose reduction in 1% of patients and discontinuation of treatment with KYPROLIS in < 1% of patients. Monitor platelet counts frequently during treatment with KYPROLIS. Reduce or interrupt dose as clinically indicated.

Hepatic Toxicity and Hepatic Failure: Cases of hepatic failure, including fatal cases, have been reported (< 1%). KYPROLIS can cause elevations of serum transaminases and bilirubin. Withhold KYPROLIS in patients experiencing Grade 3 or greater elevations of transaminases, bilirubin, or other liver enzyme abnormalities until resolved or returned to baseline. After resolution, consider if restarting KYPROLIS is appropriate. Monitor liver enzymes frequently.

Embryo-fetal Toxicity: KYPROLIS can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using KYPROLIS. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose. Females of reproductive potential should be advised to avoid becoming pregnant while being treated with KYPROLIS.

ADVERSE REACTIONS

Serious adverse reactions were reported in 45% of patients. The most common serious adverse reactions were pneumonia (10%), acute renal failure (4%), pyrexia (3%), and congestive heart failure (3%). Adverse reactions leading to discontinuation of KYPROLIS occurred in 15% of patients and included congestive heart failure (2%), cardiac arrest, dyspnea, increased blood creatinine, and acute renal failure (1% each).

The most common adverse reactions (incidence ≥ 30%) were fatigue (56%), anemia (47%), nausea (45%), thrombocytopenia (36%), dyspnea (35%), diarrhea (33%), and pyrexia (30%).

USE IN SPECIFIC POPULATIONS

Since dialysis clearance of KYPROLIS concentrations has not been studied, the drug should be administered after the dialysis procedure.

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

ONYX PHARMACEUTICALS

Kyprolis™ (carfilzomib) for Injection

KYPROLIS™ (carfilzomib) for Injection
Brief Summary of Prescribing Information. Please see the KYPROLIS package insert for full prescribing information.

INDICATIONS AND USAGE: KYPROLIS is indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate [see *Clinical Studies* section of full PI]. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

DOSAGE AND ADMINISTRATION: Dosing Guidelines. KYPROLIS is administered intravenously over 2 to 10 minutes, on two consecutive days, each week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). Each 28-day period is considered one treatment cycle (Table 1). In Cycle 1, KYPROLIS is administered at a dose of 20 mg/m^2. If tolerated in Cycle 1, the dose should be escalated to 27 mg/m^2 beginning in Cycle 2 and continued at 27 mg/m^2 in subsequent cycles. Treatment may be continued until disease progression or until unacceptable toxicity occurs [see *Dosage and Administration*]. The dose is calculated using the patient's actual body surface area at baseline. Patients with a body surface area greater than 2.2 m^2 should receive a dose based upon a body surface area of 2.2 m^2. Dose adjustments do not need to be made for weight changes of less than or equal to 20%.

Table 1: KYPROLIS Dosage Regimen for Patients with Multiple Myeloma

	Cycle 1									
	Week 1			Week 2			Week 3			Week 4
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Days 22–28
KYPROLIS (20 mg/m^2):	20	20	No Dosing	20	20	No Dosing	20	20	No Dosing	No Dosing
	Cycles 2 and Beyond[a]									
	Week 1			Week 2			Week 3			Week 4
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Days 22–28
KYPROLIS (27 mg/m^2):	27	27	No Dosing	27	27	No Dosing	27	27	No Dosing	No Dosing

[a]If previous cycle dosage is tolerated.

Hydration and Fluid Monitoring. Hydrate patients to reduce the risk of renal toxicity and of tumor lysis syndrome (TLS) with KYPROLIS treatment [see *Warnings and Precautions*]. Maintain adequate fluid volume status throughout treatment and monitor blood chemistries closely. Prior to each dose in Cycle 1, give 250 mL to 500 mL of intravenous normal saline or other appropriate intravenous fluid. Give an additional 250 mL to 500 mL of intravenous fluids as needed following KYPROLIS administration. Continue intravenous hydration, as needed, in subsequent cycles. Also monitor patients during this period for fluid overload [see *Warnings and Precautions*]. **Dexamethasone Premedication.** Pre-medicate with dexamethasone 4 mg orally or intravenously prior to all doses of KYPROLIS during Cycle 1 and prior to all KYPROLIS doses during the first cycle of dose escalation to 27 mg/m^2 to reduce the incidence and severity of infusion reactions [see *Warnings and Precautions*]. Reinstate dexamethasone premedication (4 mg orally or intravenously) if these symptoms develop or reappear during subsequent cycles. **Dose Modifications based on Toxicities.** Recommended actions and dose modifications are presented in Table 2.

Table 2: Dose Modifications for Toxicity[a] during KYPROLIS Treatment

Hematologic Toxicity	Recommended Action
• Grade 3[a] or 4 Neutropenia • Grade 4 Thrombocytopenia [see *Warnings and Precautions*]	• Withhold dose. • If fully recovered before next scheduled dose, continue at same dose level. • If recovered to Grade 2 neutropenia or Grade 3 thrombocytopenia, reduce dose by one dose level (from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2). • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Non-Hematologic Toxicity	**Recommended Action**
Cardiac Toxicity Grade 3 or 4, new onset or worsening of: • congestive heart failure; • decreased left ventricular function; • or myocardial ischemia [see *Warnings and Precautions*]	• Withhold until resolved or returned to baseline. • After resolution, consider if restarting KYPROLIS at a reduced dose is appropriate (from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2). • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Pulmonary Hypertension [see *Warnings and Precautions*]	• Withhold until resolved or returned to baseline. • Restart at the dose used prior to the event or reduced dose (from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2), at the discretion of the physician. • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Pulmonary Complications • Grade 3 or 4 [see *Warnings and Precautions*]	• Withhold until resolved or returned to baseline. • Consider restarting at the next scheduled treatment with one dose level reduction (from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2). • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Hepatic Toxicity • Grade 3 or 4 elevation of transaminases, bilirubin or other liver abnormalities [see *Warnings and Precautions*]	• Withhold until resolved or returned to baseline. • After resolution, consider if restarting KYPROLIS is appropriate; may be reinitiated at a reduced dose (from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2) with frequent monitoring of liver function. • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.

(continued)

Table 2: Dose Modifications for Toxicity[a] during KYPROLIS Treatment (continued)

Renal Toxicity • Serum creatinine equal to or greater than 2 × baseline [see *Adverse Reactions*]	• Withhold until renal function has recovered to Grade 1 or to baseline and monitor renal function. • If attributable to KYPROLIS, restart at the next scheduled treatment at a reduced dose (from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2). • If not attributable to KYPROLIS, restart at the dose used prior to the event. • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Peripheral Neuropathy • Grade 3 or 4 [see *Adverse Reactions*]	• Withhold until resolved or returned to baseline. • Restart at the dose used prior to the event or reduced dose (from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2), at the discretion of the physician. • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Other • Grade 3 or 4 non-hematological toxicities	• Withhold until resolved or returned to baseline. • Consider restarting at the next scheduled treatment with one dose level reduction (from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2). • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.

[a]National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0.

Administration Precautions. The quantity of KYPROLIS contained in one single-use vial (60 mg carfilzomib) may exceed the required dose. Caution should be used in calculating the quantity delivered to prevent overdosing. Do not mix KYPROLIS with or administer as an infusion with other medicinal products. The intravenous administration line should be flushed with normal saline or 5% Dextrose Injection, USP immediately before and after KYPROLIS administration. KYPROLIS should not be administered as a bolus. KYPROLIS should be administered over 2 to 10 minutes. **Reconstitution and Preparation for Intravenous Administration.** KYPROLIS vials contain no antimicrobial preservatives and are intended only for single use. Unopened vials of KYPROLIS are stable until the date indicated on the package when stored in the original package at 2°C to 8°C (36°F to 46°F). The reconstituted solution contains carfilzomib at a concentration of 2 mg/mL. Read the complete preparation instructions prior to reconstitution. **Reconstitution/Preparation Steps:** 1. Remove vial from refrigerator just prior to use. 2. Aseptically reconstitute each vial by slowly injecting **29 mL** Sterile Water for Injection, USP, directing the solution onto the INSIDE WALL OF THE VIAL to minimize foaming. 3. Gently swirl and/or invert the vial slowly for about 1 minute, or until complete dissolution of any cake or powder occurs. DO NOT SHAKE to avoid foam generation. If foaming occurs, allow solution to rest in vial for about 2 to 5 minutes, until foaming subsides. 4. After reconstitution, KYPROLIS is ready for intravenous administration. The reconstituted product should be a clear, colorless solution. If any discoloration or particulate matter is observed, do not use the reconstituted product. 5. When administering in an intravenous bag, withdraw the calculated dose [see *Dosage and Administration*] from the vial and dilute into **50 mL** 5% Dextrose Injection, USP intravenous bag. 6. Immediately discard the vial containing the unused portion. The stabilities of reconstituted KYPROLIS under various temperature and container conditions are shown in Table 3.

Table 3: Stability of Reconstituted KYPROLIS

Storage Conditions of Reconstituted KYPROLIS	Stability[a] per Container		
	Vial	Syringe	IV Bag (D5W[b])
Refrigerated (2°C to 8°C; 36°F to 46°F)	24 hours	24 hours	24 hours
Room Temperature (15°C to 30°C; 59°F to 86°F)	4 hours	4 hours	4 hours

[a]Total time from reconstitution to administration should not exceed 24 hours. [b]5% Dextrose Injection, USP.

WARNINGS AND PRECAUTIONS: Cardiac Arrest, Congestive Heart Failure, Myocardial Ischemia. Death due to cardiac arrest has occurred within a day of KYPROLIS administration. New onset or worsening of pre-existing congestive heart failure with decreased left ventricular function or myocardial ischemia have occurred following administration of KYPROLIS. Cardiac failure events (e.g., cardiac failure congestive, pulmonary edema, ejection fraction decreased) were reported in 7% of patients. Monitor for cardiac complications and manage promptly. Withhold KYPROLIS for Grade 3 or 4 cardiac events until recovery and consider whether to restart KYPROLIS based on a benefit/risk assessment [see *Dosage and Administration*]. Patients with New York Heart Association Class III and IV heart failure, myocardial infarction in the preceding 6 months, and conduction abnormalities uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications. **Pulmonary Hypertension.** Pulmonary arterial hypertension (PAH) was reported in 2% of patients treated with KYPROLIS and was Grade 3 or greater in less than 1% of patients. Evaluate with cardiac imaging and/or other tests as indicated. Withhold KYPROLIS for pulmonary hypertension until resolved or returned to baseline and consider whether to restart KYPROLIS based on a benefit/risk assessment [see *Dosage and Administration*]. **Pulmonary Complications.** Dyspnea was reported in 35% of patients enrolled in clinical trials. Grade 3 dyspnea occurred in 5%; no Grade 4 events, and 1 death (Grade 5) was reported. Monitor and manage dyspnea immediately; interrupt KYPROLIS until symptoms have resolved or returned to baseline [see *Dosage and Administration* and *Adverse Reactions*]. **Infusion Reactions.** Infusion reactions were characterized by a spectrum of systemic symptoms including fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of KYPROLIS. Administer dexamethasone prior to KYPROLIS to reduce the incidence and severity of reactions [see *Dosage and Administration*]. Inform patients of the risk and symptoms and to contact physician if symptoms of an infusion reaction occur [see *Patient Counseling Information*]. **Tumor Lysis Syndrome.** Tumor lysis syndrome (TLS) occurred following KYPROLIS administration in < 1% of patients. Patients with multiple myeloma and a high tumor burden should be considered to be at greater risk for TLS. Prior to receiving KYPROLIS, ensure that patients are well hydrated [see *Dosage and Administration*]. Monitor for evidence of TLS during treatment, and manage promptly. Interrupt KYPROLIS until TLS is resolved [see *Dosage and Administration*].**Thrombocytopenia.** KYPROLIS causes thrombocytopenia with platelet nadirs occurring around Day 8 of each 28-day cycle and recovery to baseline by the start of the next 28-day cycle. In patients with multiple myeloma, 36% of patients experienced thrombocytopenia, including Grade 4 in 10%. Thrombocytopenia following KYPROLIS administration resulted in a dose reduction in 1% of patients and discontinuation of treatment with KYPROLIS in < 1% of patients. Monitor platelet counts frequently during treatment with KYPROLIS. Reduce or interrupt dose as clinically indicated [see *Dosage and Administration*]. **Hepatic Toxicity and Hepatic Failure.** Cases of hepatic failure, including fatal cases, have been

reported (< 1%). KYPROLIS can cause elevations of serum transaminases and bilirubin. Withhold KYPROLIS in patients experiencing Grade 3 or greater elevations of transaminases, bilirubin, or other liver abnormalities until resolved or returned to baseline. After resolution, consider if restarting KYPROLIS is appropriate. Monitor liver enzymes frequently [see *Dosage and Administration* and *Adverse Reactions*]. **Embryo-fetal Toxicity.** KYPROLIS can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using KYPROLIS. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose. Females of reproductive potential should be advised to avoid becoming pregnant while being treated with KYPROLIS. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [see *Use in Specific Populations*].

ADVERSE REACTIONS: The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiac Arrest, Congestive Heart Failure, Myocardial Ischemia [see *Warnings and Precautions*]
- Pulmonary Hypertension [see *Warnings and Precautions*]
- Pulmonary Complications [see *Warnings and Precautions*]
- Infusion Reactions [see *Warnings and Precautions*]
- Tumor Lysis Syndrome [see *Warnings and Precautions*]
- Thrombocytopenia [see *Warnings and Precautions*]
- Hepatic Toxicity and Hepatic Failure [see *Warnings and Precautions*]

The most common adverse reactions (incidence of 30% or greater) to KYPROLIS observed in clinical trials of patients with multiple myeloma were fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia. **Clinical Trials Safety Experience.** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug, and may not reflect the rates observed in medical practice. A total of 526 patients with relapsed and/or refractory multiple myeloma received KYPROLIS as monotherapy or with pre-dose dexamethasone. Patients received a median of four treatment cycles with a median cumulative KYPROLIS dose of 993.4 mg. Deaths due to all causes within 30 days of the last dose of KYPROLIS occurred in 37/526 (7%) of patients. Deaths not attributed to disease progression were cardiac in 5 patients (acute coronary syndrome, cardiac arrest, cardiac disorder), end-organ failure in 4 patients (multi-organ failure, hepatic failure, renal failure), infection in 4 patients (sepsis, pneumonia, respiratory tract bacterial infection), dyspnea and intracranial hemorrhage in 1 patient each, and 1 patient found dead of unknown causes. Serious adverse reactions were reported in 45% patients. The most common serious adverse reactions were pneumonia (10%), acute renal failure (4%), pyrexia (3%), and congestive heart failure (3%). Adverse reactions leading to discontinuation of KYPROLIS occurred in 15% of patients and included congestive heart failure (2%), cardiac arrest, dyspnea, increased blood creatinine, and acute renal failure (1% each). Adverse reactions occurring at a rate of 10% or greater are presented in Table 4.

Table 4: Incidence of Adverse Reactions Occurring in ≥ 10% of Multiple Myeloma Patients Treated with KYPROLIS

	Patients (N = 526) [n (%)]		
Event	**All Grades[a]**	**Grade 3 Events**	**Grade 4 Events**
Fatigue	292 (55.5)	38 (7.2)	2 (0.4)
Anemia	246 (46.8)	111 (21.1)	7 (1.3)
Nausea	236 (44.9)	7 (1.3)	0
Thrombocytopenia	191 (36.3)	69 (13.1)	54 (10.3)
Dyspnea	182 (34.6)	25 (4.8)	1 (0.2)[b]
Diarrhea	172 (32.7)	4 (0.8)	1 (0.2)
Pyrexia	160 (30.4)	7 (1.3)	2 (0.4)
Upper respiratory tract infection	149 (28.3)	17 (3.2)	0
Headache	145 (27.6)	7 (1.3)	0
Cough	137 (26.0)	1 (0.2)	0
Blood creatinine increased	127 (24.1)	13 (2.5)	1 (0.2)
Lymphopenia	126 (24.0)	84 (16.0)	11 (2.1)
Edema peripheral	126 (24.0)	3 (0.6)	0
Vomiting	117 (22.2)	5 (1.0)	0
Constipation	110 (20.9)	1 (0.2)	0
Neutropenia	109 (20.7)	50 (9.5)	4 (0.8)
Back pain	106 (20.2)	15 (2.9)	0
Insomnia	94 (17.9)	0	0
Chills	84 (16.0)	1 (0.2)	0
Arthralgia	83 (15.8)	7 (1.3)	0
Muscle spasms	76 (14.4)	2 (0.4)	0
Hypertension	75 (14.3)	15 (2.9)	2 (0.4)
Asthenia	73 (13.9)	12 (2.3)	1 (0.2)
Hypokalemia	72 (13.7)	14 (2.7)	3 (0.6)
Hypomagnesemia	71 (13.5)	2 (0.4)	0
Leukopenia	71 (13.5)	27 (5.1)	1 (0.2)
Pain in extremity	70 (13.3)	7 (1.3)	0
Pneumonia	67 (12.7)	52 (9.9)	3 (0.6)[b]
Aspartate aminotransferase increased	66 (12.5)	15 (2.9)	1 (0.2)
Dizziness	66 (12.5)	5 (1.0)	1 (0.2)
Hypoesthesia	64 (12.2)	3 (0.6)	0
Anorexia	63 (12.0)	1 (0.2)	0
Pain	63 (12.0)	12 (2.3)	0
Hyperglycemia	62 (11.8)	16 (3.0)	3 (0.6)
Chest wall pain	60 (11.4)	3 (0.6)	0
Hypercalcemia	58 (11.0)	13 (2.5)	8 (1.5)
Hypophosphatemia	55 (10.5)	24 (4.6)	3 (0.6)
Hyponatremia	54 (10.3)	31 (5.9)	3 (0.6)

[a]National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0.
[b]One event was Grade 5 severity.

Description of Selected Adverse Drug Reactions. ***Renal Events:*** The most common renal adverse reactions were increase in blood creatinine (24%) and renal failure (9%), which were mostly Grade 1 or Grade 2 in severity. Grade 3 renal adverse reactions occurred in 6% of patients and Grade 4 events occurred in 1%. Discontinuations due to increased blood creatinine and acute renal failure were 1% each. In one patient, death occurred with concurrent sepsis and worsening renal function [see *Dosage and Administration*]. ***Peripheral Neuropathy:*** Peripheral neuropathy (including all events of peripheral sensory neuropathy and peripheral motor neuropathy) occurred in 14% of patients enrolled in clinical trials. Grade 3 peripheral neuropathy occurred in 1% of patients. Serious peripheral neuropathy events occurred in < 1% of patients, which resulted in dose reduction in < 1% and treatment discontinuation in < 1%. Withhold or discontinue treatment as recommended [see *Dosage and Administration*]. ***Herpes Virus Infection:*** Herpes zoster reactivation was reported in 2% of patients. Consider antiviral prophylaxis for patients who have a history of herpes zoster infection.

DRUG INTERACTIONS: Carfilzomib is primarily metabolized via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers. Carfilzomib is not expected to influence exposure of other drugs [see *Clinical Pharmacology* section of full PI].

USE IN SPECIFIC POPULATIONS: Pregnancy. Pregnancy Category D [see *Warnings and Precautions*]. Females of reproductive potential should be advised to avoid becoming pregnant while being treated with KYPROLIS. Based on its mechanism of action and findings in animals, KYPROLIS can cause fetal harm when administered to a pregnant woman. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose. If KYPROLIS is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Carfilzomib was administered intravenously to pregnant rats and rabbits during the period of organogenesis at doses of 0.5, 1, and 2 mg/kg/day in rats and 0.2, 0.4, and 0.8 mg/kg/day in rabbits. Carfilzomib was not teratogenic at any dose tested. In rabbits, there was an increase in pre-implantation loss at ≥ 0.4 mg/kg/day and an increase in early resorptions and post-implantation loss and a decrease in fetal weight at the maternally toxic dose of 0.8 mg/kg/day. The doses of 0.4 and 0.8 mg/kg/day in rabbits are approximately 20% and 40%, respectively, of the recommended dose in humans of 27 mg/m^2 based on body surface area. **Nursing Mothers.** It is not known whether KYPROLIS is excreted in human milk. Since many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from KYPROLIS, 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 KYPROLIS in pediatric patients have not been established. **Geriatric Use.** In studies of KYPROLIS there were no clinically significant differences observed in safety and efficacy between patients less than 65 years of age and patients 65 years of age and older. **Renal Impairment.** The pharmacokinetics and safety of KYPROLIS were evaluated in a Phase 2 trial in patients with normal renal function and those with mild, moderate, and severe renal impairment and patients on chronic dialysis. On average, patients were treated for 5.5 cycles using KYPROLIS doses of 15 mg/m^2 on Cycle 1, 20 mg/m^2 on Cycle 2, and 27 mg/m^2 on Cycles 3 and beyond. The pharmacokinetics and safety of KYPROLIS were not influenced by the degree of baseline renal impairment, including the patients on dialysis. Since dialysis clearance of KYPROLIS concentrations has not been studied, the drug should be administered after the dialysis procedure [see *Clinical Pharmacology* section of full PI]. **Hepatic Impairment.** The safety, efficacy and pharmacokinetics of KYPROLIS have not been evaluated in patients with baseline hepatic impairment. Patients with the following laboratory values were excluded from the KYPROLIS clinical trials: ALT/AST ≥ 3 × upper limit of normal (ULN) and bilirubin ≥ 2 × ULN [see *Clinical Pharmacology* section of full PI]. **Cardiac Impairment.** Patients with New York Heart Association Class III and IV heart failure were not eligible for the clinical trials. Safety in this population has not been evaluated.

OVERDOSAGE: There is no known specific antidote for KYPROLIS overdosage. In the event of an overdosage, monitor the patient and provide appropriate supportive care.

NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, and Impairment of Fertility. Carcinogenicity studies have not been conducted with carfilzomib. Carfilzomib was clastogenic in the *in vitro* chromosomal aberration test in peripheral blood lymphocytes. Carfilzomib was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) test and was not clastogenic in the *in vivo* mouse bone marrow micronucleus assay. Fertility studies with carfilzomib have not been conducted. No effects on reproductive tissues were noted during 28-day repeat-dose rat and monkey toxicity studies or in 6-month rat and 9-month monkey chronic toxicity studies. **Animal Toxicology and/or Pharmacology.** Monkeys administered a single bolus intravenous dose of carfilzomib at 3 mg/kg (approximately 1.3 times recommended dose in humans of 27 mg/m^2 based on body surface area) experienced hypotension, increased heart rate, and increased serum levels of troponin-T. The repeated bolus intravenous administration of carfilzomib at ≥ 2 mg/kg/dose in rats and 2 mg/kg/dose in monkeys using dosing schedules similar to those used clinically resulted in mortalities that were due to toxicities occurring in the cardiovascular (cardiac failure, cardiac fibrosis, pericardial fluid accumulation, cardiac hemorrhage/degeneration), gastrointestinal (necrosis/hemorrhage), renal (glomerulonephropathy, tubular necrosis, dysfunction), and pulmonary (hemorrhage/inflammation) systems. The dose of 2 mg/kg/dose in rats is approximately half the recommended dose in humans of 27 mg/m^2 based on body surface area. The dose of 2 mg/kg/dose in monkeys is approximately equivalent to the recommended dose in humans based on body surface area.

PATIENT COUNSELING INFORMATION: Discuss the following with patients prior to treatment with KYPROLIS: Instruct patients to contact their physician if they develop any of the following symptoms: fever, chills, rigors, chest pain, cough, or swelling of the feet or legs. Advise patients that KYPROLIS may cause fatigue, dizziness, fainting, and/or drop in blood pressure. Advise patients not to drive or operate machinery if they experience any of these symptoms. Advise patients that they may experience shortness of breath (dyspnea) during treatment with KYPROLIS. This most commonly occurs within a day of dosing. Advise patients to contact their physicians if they experience shortness of breath. Counsel patients to avoid dehydration, since patients receiving KYPROLIS therapy may experience vomiting and/or diarrhea. Instruct patients to seek medical advice if they experience symptoms of dizziness, lightheadedness, or fainting spells. Counsel females of reproductive potential to use effective contraceptive measures to prevent pregnancy during treatment with KYPROLIS. Advise the patient that if she becomes pregnant during treatment, to contact her physician immediately. Advise patients not to take KYPROLIS treatment while pregnant or breastfeeding. If a patient wishes to restart breastfeeding after treatment, advise her to discuss the appropriate timing with her physician. Advise patients to discuss with their physician any medication they are currently taking prior to starting treatment with KYPROLIS, or prior to starting any new medication(s) during treatment with KYPROLIS.

ONYX PHARMACEUTICALS

Manufactured for: Onyx Pharmaceuticals, Inc., 249 East Grand Avenue, South San Francisco, CA 94080
U.S. Patent Numbers: 7,232,818; 7,417,042; 7,491,704; 7,737,112 05-1088-00

From the Publisher

THE AMERICAN JOURNAL OF MANAGED CARE

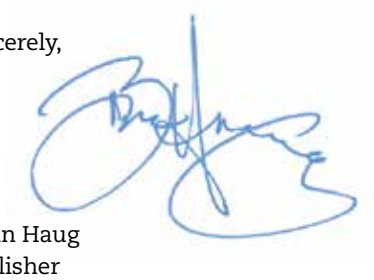
Clinical pathways have gained traction for some time now in cancer care. Culling the many treatment options available under guidelines from the National Comprehensive Cancer Network (NCCN) into narrower, evidence-based steps is the key to promoting healing while slowing soaring costs. Until now, pathways have been the province of commercial payers; for this reason, the promise they have shown has been offset by a lack of consistency. In the long run, this must be reconciled; community oncology practices, in particular, can ill afford the administrative nightmare of different pathway structures for every payer. As we report this month in *Evidence-Based Oncology*, a template may be at hand. McKesson, which owns US Oncology, discussed its hope to launch a clinical pathways pilot project with Medicare, perhaps as early as the first quarter of 2014. If this happens, it could instantly provide the framework for future pathways initiatives. Medicare's role in promoting payment for quality in cancer care cannot be overstated; as cancer patients get older, more and more of them will be relying on Medicare to pay the bills. Some estimate that 65% of all patients with cancer may be covered by Medicare by 2020. The financial stakes are enormous, both for oncology and for the government: in 2011, Medicare spent $34.4 billion for cancer care, which was 10% of its total fee-for-service payments for the year. It remains to be seen how hopes for clinical pathways in oncology will fold into the larger payment reform agenda in Washington, DC.

McKesson, which owns US Oncology, discussed its hope to launch a clinical pathways pilot project with Medicare, perhaps as early as the first quarter of 2014. If this happens, it could offer the framework for future pathways initiatives. Medicare's footprint in cancer care cannot be overstated.

This issue of *EBO* updates efforts to replace Medicare's Sustainable Growth Rate (SGR), the reimbursement tool long decried as useless. Is the latest 3-month "patch," which the Community Oncology Alliance says effectively amounts to a pay cut, the last of these Band-Aids before a cure is found? For payment reform to take hold, and with it the promise of the Affordable Care Act, lawmakers must end the years of uncertainty. Those who care for some of our most vulnerable patients have taken on too much risk in recent years, and it is time for them to gain peace of mind.

Those who attended our fall conference, Patient-Centered Oncology Care 2013, heard a moving account from Amy Berman, BS, RN, of the importance of making cancer treatment match the goals of the patient. In some cases, too much care can be as harmful as too little. Berman's perspective—that of a long-term quality care advocate facing a frightening diagnosis—points up the growing importance of the patient advocate in cancer care. This month's issue explores the emerging role of advocates, who do everything from help patients take control to find money for life-saving drugs. Please look for our supplement of the proceedings from Patient-Centered Oncology Care 2013 to complete your reading. As always, look for updates on www.ajmc.com.

Sincerely,



Brian Haug
Publisher

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.

THE AMERICAN JOURNAL OF MANAGED CARE

In This Issue...

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These are therapies that potentially could keep going and keep working following reactivation. We're actually sort of vaccinating...
Daniel J. George, MD

Not only does the combination of accelerated approval with post marketing research get drugs to market quickly, but phase IV research may lead to new indications.
Mark Crowther, MD

THE AMERICAN JOURNAL OF MANAGED CARE

A Test to Prevent Repeat Prostate Biopsies? Perhaps, if the Bar of "Clinical Utility" Can Be Met

Mary K. Caffrey

If a man who has symptoms of prostate cancer but a negative biopsy could use a test to avoid a second biopsy, wouldn't that test make sense?

It might, but it might not. The decision to pay for the test could rest on whether the man's insurer, which often is Medicare, thinks his doctor will act based solely on the test's outcome.

This is the world of "clinical utility," where in recent years, proving a test's accuracy no longer pushes it past the finish line for payers.

Recent efforts by MDxHealth, based in Hertsal, Belgium, and Irvine, California, to market its ConfirmMDx epigenetic test for prostate cancer—and to gather data to support broader availability—crystallize the competing forces at work in the molecular diagnostic marketplace, as clinical utility has emerged as the new bar for reimbursement.

Why the change? It comes down to a single word: Cost.

In the decade after the sequencing of the human genome, there's been an explosion in personalized medicine, along with a rapid rise in new cost categories that didn't exist just a few years ago.[1]

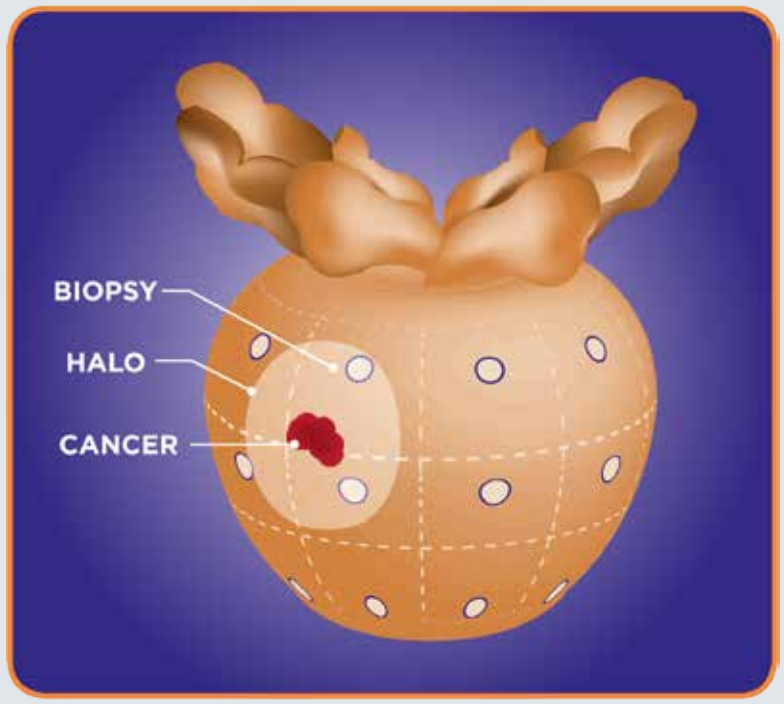
A March 2012 white paper published by UnitedHealthcare said the payer spent $500 million on genetic and diagnostic testing in 2010, which represented 14% more per person than in 2008. Extrapolating on its own data, United Healthcare pegged the 2010 total for Medicaid and Medicare at $5 billion, or 8% of all national spending on clinical laboratory tests.[2]

The concept of personalized medicine—matching the right drug to the right patient at the right time—holds out the promise of driving down costs over time, as therapies are used with precision, leaving less waste and fewer side effects. But for a test like ConfirmMDx to save money demands that physicians practice medicine differently, relying on a test *instead* of a second biopsy.[3]

As new genetic and biomarker-based tests emerge, not all payers are convinced that physicians are ready for change. The bar of clinical utility requires test makers to prove that their diagnostic tool is *the* factor that drives decisions, not a belt-and-suspenders add-on that simply gives doctors more information.

Therein lies the conundrum. Beth Davis, senior director of health policy and reimbursement for MDxHealth, said "clinical utility" means showing that a test has value to doctors in real-world settings. And proving that value can be difficult if payers won't reimburse for the test, because that has the practical effect of making it unavailable to most patients.

Figure. How the Epigenetic Test Works



ConfirmMDx detects an epigenetic field effects or "halo" associated with the presence of cancer at the DNA level. This epigenetic "halo" around a cancer lesion can be present despite having a normal appearance under the microscope (Stewart GD, Van Neste L, Delvenne P et al. Clinical utility of an epigenetic assay to detect occult prostate cancer in histopathologically negative biopsies: results of the MATLOC study. *J Urol.* 2013;189(3):1110-1116).

Image courtesy of MDxHealth, Irvine, California.

Clinical utility, Davis said, "is a big, evolving discussion right now, because it means different things to different people." Essentially, she said, "You're measuring physician behavior."

In the case of ConfirmMDx, the test maker is not only making the clinical argument that the test works, but also the economic argument that it saves money by preventing unnecessary second and third biopsies. Davis made her case December 4, 2013, at the Philadelphia meeting, Oral Oncolytics, including data that show 700,000 men have repeat biopsies annually because the standard 12-core method can miss a growing cancer[3,4] (**See Figure**).

Used in lieu of repeat biopsies, ConfirmMDx could save $588 per patient on average, or $500,000 a year for a commercial health plan with 1 million members, according to results published in *American Health & Drug Benefits*.[5] The MDxHealth website has a growing list of commercial plans that reimburse for the test, and it continues to highlight results about the test's validity.[6,7]

An Economic and Quality of Life Case

Prostate is the most common cancer among men, except for skin cancer; it is the leading cause of cancer deaths among men behind lung cancer. The American Cancer Society estimated that 238,590 new cases would be diagnosed in 2013, with 29,720 deaths.[8]

At the same time, the rise of cancer screening with the prostate-specific antigen (PSA) test over the past 20 years means that 2.5 million men who have had prostate cancer are alive today.[8]

Widespread screening has saved lives but also increased costs and for some, complications. There is increased promotion of a "wait and watch" approach to those tumors that are not aggressive, and questions about the value of PSA testing led the US Preventive Services Task Force (USPSTF) to issue a highly controversial D rating for the popular screening.[9] (**See Panel Discussion, next page**).

Since most prostate cancer diagnoses occur among older men, cost implications of large-scale PSA testing are huge. A study published just this month in *Cancer* tracked almost 95,000 men in Medicare, aged 66 to 99 years, who had never had prostate cancer, for 3 years.[10] Just over half, or 51.2%, had PSA tests during the period, with 2.9% having a biopsy.[10]

But as the *Cancer* article noted, 72% of the costs associated with PSA screening came from "downstream biopsy-related procedures,"[10] and not from the screening itself; if those costs could be mitigated, discussion over the controversial D rating from the USPSTF might shift from how to not screen to how to limit the number of biopsies that result.

ConfirmMDx still relies on biopsy as what Davis called the "gold standard," but it recognizes that the standard 12-core method might miss cancerous tissue. ConfirmMDx seeks to confirm the presence of an epigenetic "halo" that exists around a tumor, which might be present even though the cells look normal under a microscope.

The test relies upon DNA methylation, a biochemical process that can alter gene expression as cells divide and result in the silencing of tumor suppressors. When DNA methylation goes awry, unfolding either too quickly or too slowly, cancer can result. This process does not happen all at once; thus, DNA methylation can be used as a readout for a pre-cancerous or cancerous state.

If a patient has a negative biopsy but a positive result with ConfirmMDx, the doctor can either treat as if the patient had a positive pathology result, or limit additional cores to the area of known "hot spots," reducing costs, discomfort, and side effects, according to Davis. Thus, the ConfirmMDx test can not only limit costs but also improve quality of life.

Epigenetic test results may also help determine how aggressive the prostate cancer is and guide treatment, based on data presented at the American Society of Clinical Oncology Genitourinary (ASCO GU) Cancers Symposium in San Francisco on January 31, 2014. In the results, low methylation levels corresponded to low Gleason scores[11]; this is significant because the same material collected at biopsy and used to determine if treatment is needed could also be used to determine if the cancer is aggressive, Davis confirmed.

Given the uproar over the USPSTF rating of D, however, multiple methods are emerging to spot prostate cancer and gauge its aggressiveness. On the detection front, a study published just this month in *Radiology* examined the use of multiparametric magnetic resonance (MR) imaging to detect prostate cancers in low-risk patients.[12] Not surprisingly, researchers found that MR imaging was more reliable in detecting larger cancers (1 cm^3 and Gleason score of 7 or above) than smaller cancers, but was reliable overall.[12]

ConfirmMDx has competition in the realm of testing for cancer aggressiveness. At the same ASCO GU symposium, Myriad Genetics presented results from the PROCEDE 500 registry study, which measured clinical utility for its cell-cycle progression signature test, marketed as Prolaris. So far, data are available on 294 patients across 15 urology practices, with physicians indicating that test results would lead to a definite or possible change in 32% of cases.[13]

Emerging Standards for Diagnostic Tests

A discussion of clinical utility appeared in the literature in December 2010, when Bruce Quinn MD, PhD, an influential contributor to discussions of payment reform in Medicare and Medicaid, wrote an article in *Clinical Pharmacology and Therapeutics* that addressed decision-making frameworks for payers to use when evaluating companion diagnostics.[14]

Over the course of 2011, the ground shifted for test makers from clinical validity, which asks whether the test correctly measures what it is supposed to measure, to clinical utility, which asks if the test is the critical item that guides or even changes physician behavior.

By 2012, the Baltimore-based Center for Medical Technology Policy (CMTP) began an effort to develop an Effectiveness Guidance Document, or EGD, in the area of molecular diagnostic testing.[15] This process, which was supported by leaders in the pharmaceutical and diagnostic testing industries as well as by payers, represented a multi-stakeholder effort to develop criteria for evaluating tests used in personalized medicine.

A report published May 1, 2013, outlines in its executive summary 10 items in the areas of reporting, clinical validity, and clinical utility to be used when evaluating tests, and notes that the very nature of such tests requires innovative payment approaches, including some that must be approved on a case-by-case basis.[15]

Davis noted that clinical utility is only measured after a diagnostic test is commercially available. "For diagnostics in general, it can sometimes be more difficult to prospectively randomize testing due to variance in practice," with urology being a good example, she said. The CMTP report, she said, provides a "balanced framework" for creating avenues for reimbursement while evidence of clinical utility is still being developed. **EBO**

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Panel Discussion

Sorting Out What Makes Sense in Diagnosing, Treating Prostate Cancer

Produced by Nicole Beagin

In the fall, *The American Journal of Managed Care* convened an expert panel to address emerging issues in the treatment of prostate cancer. According to a 2012 report from the American Cancer Society, prostate cancer is the most common cancer among men, accounting for 43% of all cancer cases among men in the United States.[1] Panelists addressed current controversies over when and how often to screen men for prostate cancer, as well as which treatments should be given to which patients. This transcript has been condensed.

The discussion was chaired by **A. Mark Fendrick, MD,** co-editor-in-chief of *The American Journal of Managed Care*. Participants were:

- E. David Crawford, MD, head of Urologic Oncology at The University of Colorado at Denver, University of Colorado Hospital,
- Daniel J. George, MD, Duke Cancer Institute, and
- Neal Shore, MD, medical director, The Carolina Urologic Research Center, Myrtle Beach, SC.

Prostate Cancer Screening: Is the PSA Test Still Valuable?

A. Mark Fendrick, MD, opened the discussion by asking panelists to respond to the controversy surrounding the 2011 recommendation from the US Preventive Services Task Force (USPSTF), which called for not screening men without symptoms using the prostate-specific antigen (PSA) test.[2] The recommendation has been criticized in some circles and was followed with a separate recommendation from the American Urological Association (AUA) that screening on asymptomatic men not occur until 55 years.[3] As Fendrick explained, the apparent competing recommendations "have made it quite confusing for general internists like myself," as well as stakeholders—including payers who must decide whether the PSA test will be covered. Dr Fendrick invited comment from Neal Shore, MD, and E. David Crawford, MD. Dr Crawford has published on this topic and is currently involved in the PLCO trial (prostate, lung, colorectal, and ovarian screening).

Dr Crawford: This is one of the more controversial areas in prostate cancer and early detection. In 1989, prostate cancer became the most common cancer in American men, and the second-leading cause of death. Most of the cases that were diagnosed were advanced. When the maximum PSA test came out, the thinking was that mortality rates could be reduced with screening for early detection.

What happened was we were too successful—the pendulum swung from late diagnosis to an over-diagnosis of cancer. We were finding small cancers and overtreating people. The real controversy is very simple, I think, you need to separate diagnosis from treatment.…

(continued on SP35)

IN MBC, ONCOLOGISTS ARE CONSISTENTLY
EXTENDING THE CONTINUUM OF MEANINGFUL CARE[1-3]

With MBC treatment potentially extending to 6 lines and beyond, third-line chemotherapy can still be early in the fight for some patients[2]

MBC=metastatic breast cancer.

Indication

Halaven is indicated for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.

Important Safety Information

Neutropenia

- Monitor complete blood counts prior to each dose, and increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting longer than 7 days
- Severe neutropenia (ANC <500/mm^3) lasting more than 1 week occurred in 12% (62/503) of patients. Patients with elevated liver enzymes >3 × ULN and bilirubin >1.5 × ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal levels
- Grade 3 and Grade 4 neutropenia occurred in 28% and 29%, respectively, of patients who received Halaven. Febrile neutropenia occurred in 5% of patients and two patients (0.4%) died from complications

Peripheral Neuropathy

- Patients should be monitored closely for signs of peripheral motor and sensory neuropathy
- Grade 3 peripheral neuropathy occurred in 8% of patients, and Grade 4 in 0.4% of patients who received Halaven. Delay administration of Halaven until resolution to Grade 2 or less
- Neuropathy lasting more than 1 year occurred in 5% of patients. Twenty-two percent of patients developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25-662 days)
- Peripheral neuropathy (5%) was the most common adverse reaction resulting in discontinuation

Pregnancy Category D

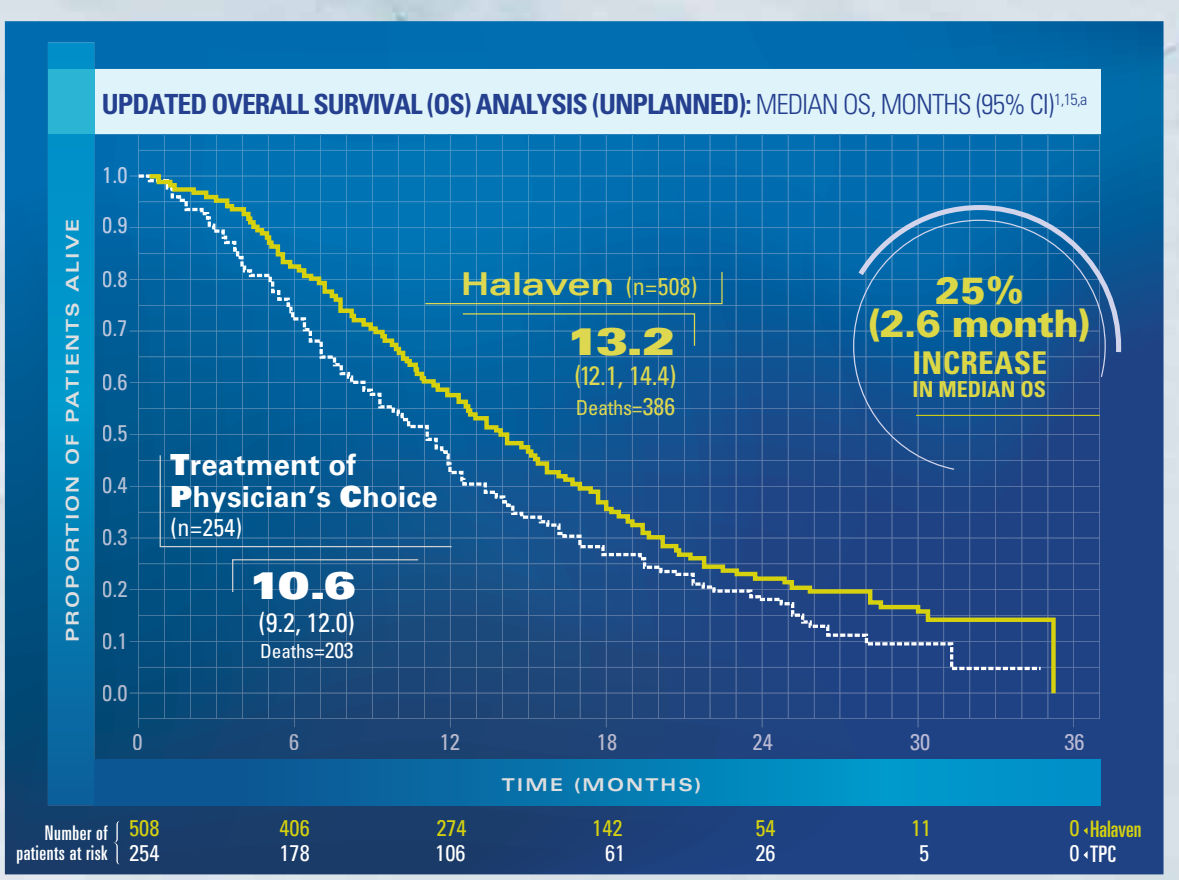
- Halaven is expected to cause fetal harm when administered to a pregnant woman and patients should be advised of these risks

QT Prolongation

- In an uncontrolled ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no prolongation on Day 1. ECG monitoring is recommended for patients with congestive heart failure; bradyarrhythmias;

GIVE YOUR PATIENTS AN OPPORTUNITY FOR MORE LIFE

The FIRST and ONLY single agent that significantly extended OVERALL SURVIVAL in third-line MBC[7-14]



Results from an updated, unplanned survival analysis of the Phase III, randomized, open-label, multicenter, multinational Eisai Metastatic Breast Cancer Study Assessing Physician's Choice versus E7389 (Eribulin) (EMBRACE) trial of Halaven versus Treatment of Physician's Choice (TPC) in patients with MBC (N=762), conducted when 77% of events (deaths) had been observed. The primary endpoint was OS. Patients were randomized (2:1) to receive either Halaven 1.4 mg/m^2 intravenously for 2 to 5 minutes on Days 1 and 8 of a 21-day cycle, or any single-agent therapy, selected prior to randomization. At baseline, all patients had received ≥2 prior chemotherapeutic regimens for metastatic disease and demonstrated disease progression within 6 months of their last chemotherapeutic regimen. All patients received prior anthracycline- and taxane-based chemotherapy, unless contraindicated. Therapies in the TPC arm consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxanes [included paclitaxel, docetaxel, nab-paclitaxel, and ixabepilone], 9% anthracyclines, 10% other chemotherapy), and 3% hormonal therapy.

CI=confidence interval.
[a]Conducted in the intent-to-treat population.

The updated OS analysis was consistent with the primary analysis[7]

- The primary analysis, conducted when ~50% of events (deaths) had been observed, demonstrated a median OS for Halaven vs TPC of 13.1 months (95% CI: 11.8, 14.3) vs 10.6 months (95% CI: 9.3, 12.5), hazard ratio=0.81 (95% CI: 0.66, 0.99) (*P*=0.041)[7,15]

concomitant use of drugs that prolong QT interval, including Class Ia and III antiarrhythmics; and electrolyte abnormalities

- Correct hypokalemia or hypomagnesemia prior to initiating Halaven and monitor electrolytes periodically during therapy. Avoid in patients with congenital long QT syndrome

Hepatic and Renal Impairment

- For patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic and/or moderate (CrCl 30-50 mL/min) renal impairment, a reduction in starting dose is recommended

Most Common Adverse Reactions

- Most common adverse reactions (≥25%) reported in patients receiving Halaven were neutropenia (82%), anemia (58%), asthenia/fatigue (54%), alopecia (45%), peripheral neuropathy (35%), nausea (35%), and constipation (25%)
- The most common serious adverse reactions reported in patients receiving Halaven were febrile neutropenia (4%) and neutropenia (2%)

References: 1. Dufresne A, et al. *Breast Cancer Res Treat.* 2008;107(2):275-279. **2.** Planchat E, et al. *Breast.* 2011;20(6):574-578. **3.** Ray S, et al. In: *J Clin Oncol.* San Francisco, CA: ASCO Breast Cancer Symposium; 2012. Abstract 116. **4.** Cardoso F, et al. *Ann Oncol.* 2002;13(2):197-207. **5.** Seah DS, et al. Poster presented at: 2012 ASCO Annual Meeting; June 1–5, 2012; Chicago, IL. Abstract 6089. **6.** Lin NU, et al. *Lancet.* 2011;377(9769):878-880. **7.** Halaven [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2013. **8.** Saad ED, et al. *J Clin Oncol.* 2010;28(11):1958-1962. **9.** Slamon DJ, et al. *N Engl J Med.* 2001;344(11):783-792. **10.** Geyer CE, et al. *N Engl J Med.* 2006;355(26):2733-2743. **11.** von Minckwitz G, et al. *J Clin Oncol.* 2009;27(12):1999-2006. **12.** Miller K, et al. *N Engl J Med.* 2007;357(26):2666-2676. **13.** Robert NJ, et al. *J Clin Oncol.* 2011;29(10):1252-1260. **14.** Sparano JA, et al. *J Clin Oncol.* 2010;28(20):3256-3263. **15.** Cortes J, et al. *Lancet.* 2011;377(9769):914-923.

Please see accompanying brief summary of Halaven full Prescribing Information.

Visit **www.halaven.com/hcp.aspx**

Halaven®
(eribulin mesylate) Injection
ADVANCING SURVIVAL

HALAVEN® (eribulin mesylate) Injection BRIEF SUMMARY – See package insert for full prescribing information.

2.2 Dose Modification

Assess for peripheral neuropathy and obtain complete blood cell counts prior to each dose.

Recommended dose delays

- Do not administer HALAVEN on Day 1 or Day 8 for any of the following:
  - ANC <1,000/mm^3
  - Platelets <75,000/mm^3
  - Grade 3 or 4 non-hematological toxicities.
- The Day 8 dose may be delayed for a maximum of 1 week.
  - If toxicities do not resolve or improve to ≤ Grade 2 severity by Day 15, omit the dose.
  - If toxicities resolve or improve to ≤ Grade 2 severity by Day 15, administer HALAVEN at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

Recommended dose reductions

- If a dose has been delayed for toxicity and toxicities have recovered to Grade 2 severity or less, resume HALAVEN at a reduced dose as set out in Table 1.
- Do not re-escalate HALAVEN dose after it has been reduced.

Table 1 Recommended Dose Reductions

Event Description	Recommended HALAVEN Dose
Permanently reduce the 1.4 mg/m^2 HALAVEN dose for any of the following:	1.1 mg/m^2
ANC <500/mm^3 for >7 days	
ANC <1,000 /mm^3 with fever or infection	
Platelets <25,000/mm^3	
Platelets <50,000/mm^3 requiring transfusion	
Non-hematologic Grade 3 or 4 toxicities	
Omission or delay of Day 8 HALAVEN dose in previous cycle for toxicity	
Occurrence of any event requiring permanent dose reduction while receiving 1.1 mg/m^2	0.7 mg/m^2
Occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m^2	Discontinue HALAVEN

ANC = absolute neutrophil count.

Toxicities graded in accordance with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

5 WARNINGS AND PRECAUTIONS

5.1 Neutropenia

Severe neutropenia (ANC <500/mm^3) lasting more than one week occurred in 12% (62/503) of patients in Study 1, leading to discontinuation in <1% of patients. Patients with alanine aminotransferase or aspartate aminotransferase >3 × ULN (upper limit of normal) experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal aminotransferase levels. Patients with bilirubin >1.5 × ULN also had a higher incidence of Grade 4 neutropenia and febrile neutropenia.

Monitor complete blood counts prior to each dose; increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration of HALAVEN and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting longer than 7 days. Clinical studies of HALAVEN did not include patients with baseline neutrophil counts below 1,500/mm^3.

5.2 Peripheral Neuropathy

Grade 3 peripheral neuropathy occurred in 8% (40/503) of patients, and Grade 4 in 0.4% (2/503) of patients in Study 1. Peripheral neuropathy was the most common toxicity leading to discontinuation of HALAVEN (5% of patients; 24/503). Neuropathy lasting more than one year occurred in 5% (26/503) of patients. Twenty-two percent (109/503) of patients developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25-662 days). Monitor patients closely for signs of peripheral motor and sensory neuropathy. Withhold HALAVEN in patients who experience Grade 3 or 4 peripheral neuropathy until resolution to Grade 2 or less.

5.3 Embryo-Fetal Toxicity

There are no adequate and well-controlled studies of HALAVEN in pregnant women. HALAVEN is a microtubule inhibitor; therefore, it is expected to cause fetal harm when administered to a pregnant woman. Embryo-fetal toxicity and teratogenicity occurred in rats that received eribulin mesylate at approximately half of the recommended human dose based on body surface area. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.

5.4 QT Prolongation

In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating HALAVEN and monitor these electrolytes periodically during therapy. Avoid HALAVEN in patients with congenital long QT syndrome.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

• Neutropenia • Peripheral neuropathy • QT interval prolongation

The most common adverse reactions (≥25%) reported in patients receiving HALAVEN were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common serious adverse reactions reported in patients receiving HALAVEN were febrile neutropenia (4%) and neutropenia (2%). The most common adverse reaction resulting in discontinuation of HALAVEN was peripheral neuropathy (5%).

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

In clinical trials, HALAVEN has been administered to 1,222 patients with multiple tumor types, including 240 patients exposed to HALAVEN for 6 months or longer. The majority of the 1,222 patients were women (82%) with a median age of 58 years (range: 26 to 91 years). The racial and ethnic distribution was Caucasian (83%), Black (5%), Asian (2%), and other (5%).

The adverse reactions described in Table 2 were identified in 750 patients treated in Study 1. In Study 1, patients were randomized (2:1) to receive either HALAVEN (1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle) or single agent treatment chosen by their physician (control group). A total of 503 patients received HALAVEN, and 247 patients in the control group received therapy consisting of chemotherapy [total 97% (anthracyclines 10%, capecitabine 18%, gemcitabine 19%, taxanes 15%, vinorelbine 25%, other chemotherapies 10%)] or hormonal therapy (3%). The median duration of exposure was 118 days for patients receiving HALAVEN and 63 days for patients receiving control therapy. Table 2 reports the most common adverse reactions occurring in at least 10% of patients in either group.

Table 2 Adverse Reactions with a Per-Patient Incidence of at Least 10% in Study 1

MedDRA ver 10.0	HALAVEN (n=503)		Control Group (n=247)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Blood and Lymphatic System Disorders[a]				
Neutropenia	82%	57%	53%	23%
Anemia	58%	2%	55%	4%
Nervous system disorders				
Peripheral neuropathy[b]	35%	8%	16%	2%
Headache	19%	<1%	12%	<1%
General disorders and administrative site conditions				
Asthenia/Fatigue	54%	10%	40%	11%
Mucosal inflammation	9%	1%	10%	2%
Pyrexia	21%	<1%	13%	<1%
Gastrointestinal disorders				
Constipation	25%	1%	21%	1%
Diarrhea	18%	0	18%	0
Nausea	35%	1%	28%	3%
Vomiting	18%	1%	18%	1%
Musculoskeletal and connective tissue disorders				
Arthralgia/Myalgia	22%	<1%	12%	1%
Back pain	16%	1%	7%	2%
Bone pain	12%	2%	9%	2%
Pain in extremity	11%	1%	10%	1%
Investigations				
Weight decreased	21%	1%	14%	<1%
Metabolism and nutrition disorders				
Anorexia	20%	1%	13%	1%
Respiratory, thoracic, and mediastinal disorders				
Cough	14%	0	9%	0
Dyspnea	16%	4%	13%	4%
Skin and subcutaneous tissue disorders				
Alopecia	45%	NA[c]	10%	NA[c]

Table 2 (cont'd)

MedDRA ver 10.0	HALAVEN (n=503)		Control Group (n=247)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Infections and Infestations				
Urinary Tract Infection	10%	1%	5%	0

[a] Based upon laboratory data.

[b] Includes neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paraesthesia.

[c] Not applicable; (grading system does not specify > Grade 2 for alopecia).

Cytopenias: Grade 3 neutropenia occurred in 28% (143/503) of patients who received HALAVEN in Study 1, and 29% (144/503) of patients experienced Grade 4 neutropenia. Febrile neutropenia occurred in 5% (23/503) of patients; two patients (0.4%) died from complications of febrile neutropenia. Dose reduction due to neutropenia was required in 12% (62/503) of patients and discontinuation was required in <1% of patients. The mean time to nadir was 13 days and the mean time to recovery from severe neutropenia (<500/mm^3) was 8 days. Grade 3 or greater thrombocytopenia occurred in 1% (7/503) of patients. G-CSF (granulocyte colony-stimulating factor) or GM-CSF (granulocyte–macrophage colony-stimulating factor) was used in 19% of patients who received HALAVEN.

Peripheral Neuropathy: In Study 1, 17% of enrolled patients had Grade 1 peripheral neuropathy and 3% of patients had Grade 2 peripheral neuropathy at baseline. Dose reduction due to peripheral neuropathy was required by 3% (14/503) of patients who received HALAVEN. Four percent (20/503) of patients experienced peripheral motor neuropathy of any grade and 2% (8/503) of patients developed Grade 3 peripheral motor neuropathy.

Liver Function Test Abnormalities: Among patients with Grade 0 or 1 ALT levels at baseline, 18% of HALAVEN-treated patients experienced Grade 2 or greater ALT elevation. One HALAVEN-treated patient without documented liver metastases had concomitant Grade 2 elevations in bilirubin and ALT; these abnormalities resolved and did not recur with re-exposure to HALAVEN.

Less Common Adverse Reactions: The following additional adverse reactions were reported in ≥5% to <10% of the HALAVEN-treated group: **Eye Disorders:** increased lacrimation; **Gastrointestinal Disorders:** dyspepsia, abdominal pain, stomatitis, dry mouth; **General Disorders and Administration Site Conditions:** peripheral edema; **Infections and Infestations:** upper respiratory tract infection; **Metabolism and Nutrition Disorders:** hypokalemia; **Musculoskeletal and Connective Tissue Disorders:** muscle spasms, muscular weakness; **Nervous System Disorders:** dysgeusia, dizziness; **Psychiatric Disorders:** insomnia, depression; **Skin and Subcutaneous Tissue Disorders:** rash.

6.2 Postmarketing Experience

The following adverse drug reactions have been identified during post-approval of HALAVEN. 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. **Blood and Lymphatic System Disorders:** lymphopenia; **Gastrointestinal Disorders:** pancreatitis; **Hepatobiliary Disorders:** hepatitis; **Immune System Disorders:** drug hypersensitivity; **Infections and Infestations:** pneumonia, sepsis/neutropenic sepsis; **Metabolism and Nutrition Disorders:** hypomagnesemia, dehydration; **Respiratory, thoracic, and mediastinal disorders:** interstitial lung disease; **Psychiatric Disorders:** anxiety; **Skin and Subcutaneous Tissue Disorders:** pruritus.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Category D

There are no adequate and well-controlled studies with HALAVEN in pregnant women. HALAVEN is a microtubule inhibitor; therefore, it is expected to cause fetal harm when administered to a pregnant woman. Embryo-fetal toxicity and teratogenicity occurred in rats that received eribulin mesylate at approximately half of the recommended human dose based on body surface area. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

In a developmental toxicity study, pregnant rats received intravenous infusion of eribulin mesylate during organogenesis (Gestation Days 8, 10, and 12) at doses approximately 0.04, 0.13, 0.43 and 0.64 times the recommended human dose, based on body surface area (mg/m^2). Increased abortion and severe external or soft tissue malformations were observed in offspring at doses 0.64 times the recommended human dose based on body surface area (mg/m^2), including the absence of a lower jaw, tongue, stomach and spleen. Increased embryo-fetal death/resorption, reduced fetal weights, and minor skeletal anomalies consistent with developmental delay were also reported at or above doses of 0.43 times the recommended human dose.

Maternal toxicity of eribulin mesylate was reported in rats at or above doses of 0.43 times the recommended human dose (mg/m^2), and included enlarged spleen, reduced maternal weight gain and decreased food consumption.

8.3 Nursing Mothers

It is not known whether HALAVEN is excreted into human milk. No studies in humans or animals were conducted to determine if HALAVEN is excreted into milk. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in human milk fed infants from HALAVEN, a decision should be made whether to discontinue nursing or to discontinue HALAVEN taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of HALAVEN in pediatric patients below the age of 18 years have not been established.

8.6 Hepatic Impairment

Administration of HALAVEN at a dose of 1.1 mg/m^2 to patients with mild hepatic impairment and 0.7 mg/m^2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m^2 to patients with normal hepatic function. Therefore, a lower starting dose of 1.1 mg/m^2 is recommended for patients with mild hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh B). HALAVEN was not studied in patients with severe hepatic impairment (Child-Pugh C).

8.7 Renal Impairment

For patients with moderate renal impairment (CrCl 30-50 mL/min), the geometric mean dose-normalized systemic exposure increased 2-fold compared to patients with normal renal function. A lower starting dose of 1.1 mg/m^2 is recommended for patients with moderate renal impairment. The safety of HALAVEN was not studied in patients with severe renal impairment (CrCl <30 mL/min).

10 OVERDOSAGE

Overdosage of HALAVEN has been reported at approximately 4 times the recommended dose, which resulted in Grade 3 neutropenia lasting seven days and a Grade 3 hypersensitivity reaction lasting one day.

There is no known antidote for HALAVEN overdose.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Specific Populations

Hepatic Impairment

A study evaluated the PK of eribulin in patients with mild (Child-Pugh A; n=7) and moderate (Child-Pugh B; n=5) hepatic impairment. Compared to patients with normal hepatic function (n=6), eribulin exposure increased 1.8-fold and 2.5-fold in patients with mild and moderate hepatic impairment, respectively. Administration of HALAVEN at a dose of 1.1 mg/m^2 to patients with mild hepatic impairment and 0.7 mg/m^2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m^2 to patients with normal hepatic function.

Renal Impairment

No formal PK trials were conducted with HALAVEN in patients with renal impairment. Available data suggests that geometric mean dose-normalized systemic exposure is similar for patients with mild renal impairment (CrCl 50-80 mL/min) relative to patients with normal renal function. However, for patients with moderate renal impairment (CrCl 30-50 mL/min), the geometric mean dose-normalized systemic exposure increased 2-fold compared to patients with normal renal function.

12.6 Cardiac Electrophysiology

The effect of HALAVEN on the QTc interval was assessed in an open-label, uncontrolled, multicenter, single-arm dedicated QT trial. A total of 26 patients with solid tumors received 1.4 mg/m^2 of HALAVEN on Days 1 and 8 of a 21-day cycle. A delayed QTc prolongation was observed on Day 8, with no prolongation observed on Day 1. The maximum mean QTcF change from baseline (95% upper confidence interval) was 11.4 (19.5) ms.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenicity studies have not been conducted with eribulin mesylate.

Eribulin mesylate was not mutagenic in *in vitro* bacterial reverse mutation assays (Ames test). Eribulin mesylate was positive in mouse lymphoma mutagenesis assays, and was clastogenic in an *in vivo* rat bone marrow micronucleus assay.

The effects of HALAVEN on human fertility are unknown. Fertility studies have not been conducted with eribulin mesylate in humans or animals. However, nonclinical findings in repeated-dose dog and rat toxicology studies suggest that male fertility may be compromised by treatment with eribulin mesylate. Rats exhibited testicular toxicity (hypocellularity of seminiferous epithelium with hypospermia/aspermia) following dosing with eribulin mesylate at or above 0.43 times the recommended human dose (mg/m^2) given once weekly for 3 weeks, or at or above 0.21 times the recommended human dose (mg/m^2) given once weekly for 3 out of 5 weeks, repeated for 6 cycles. Testicular toxicity was also observed in dogs given 0.64 times the recommended human dose (mg/m^2) weekly for 3 out of 5 weeks, repeated for 6 cycles.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

- Advise patients to contact their health care provider for a fever of 100.5°F or greater or other signs or symptoms of infection such as chills, cough, or burning or pain on urination.
- Advise women of childbearing potential to avoid pregnancy and to use effective contraception during treatment with HALAVEN.

Eisai

(continued from SP31)

The backlash occurred, and it needed to occur, but now we need to get some equilibrium and really identify who will benefit from treatment. Thirty thousand men are still dying from prostate cancer, and we need to whittle away at that.

Dr Shore: I completely agree. We have this conundrum: We have many patients who do not need treatment, and yet we have many patients who need aggressive treatment. We have 250,000 men who get newly diagnosed with prostate cancer, and much of the data would suggest anywhere from 30 to 50% have a very unaggressive or low-grade form of the disease and would benefit from monitoring, or what some call active surveillance. We have not done a great job of that, but we now are on the cusp of doing a much better job with additional biomarkers and assays.

At the same time, there are 50 to 60% of men who need active interventional treatment, whether it is surgical removal or radiation or cryoablation. And so the task force recommendation of D (which states there is "moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits") has uniformly been met with disdain and shock by the urologic community, because it was just too severe.

The Large Urology Group Practice Association will have additional recommendations that will give greater clarity and specificity, to help the clinicians better understand that PSA does have value if used judiciously.

Table. New Therapies for Prostate Cancer Treatment

Drug	Approval Date	Mechanism of Action
Arbiterone acetate (Zytiga) plus Prednisone	April 28, 2011	Selective CYP17 inhibitor
Enzalutamide (Xtandi)	August 31, 2012	Prevents androgen binding to androgen receptor (AR). Inhibits androgen-dependent nuclear translocation of AR. Inhibits androgen-dependent AR association with the DNA. Inhibits proliferation and induces cell death in PC cells.
Sipuleucel-T (Provenge)	April 29, 2010	Immune response targeted against PAP (prostatic acid phosphatase), a cellular antigene expressed in most PC cells.
Cabazitaxel injection (Jevtana Kit)	June 17, 2010	Microtubule inhibitor that binds tubulin, promotes microtubule polymerization, and prevents dissassembly. Stabilizes microtubules, which results in the inhibition of mitotic and interphase cell functions.
Radium RA-223 dichloride injection (Xofigo)	May 15, 2013	RA-223, an α particle emitter, is a calcium mimetic that complexes with hydroxyapatite in areas of increased bone turnover (like metasatic regions). The resulting energy transfer causes double strand DNA breaks, which in turn results in cytotoxicity and cell cycle arrest, and inhibits osteoclast differentiation and osteoblast activity in vitro.
Cabozantinib S-Malate (Cometriq) *(Approved for thyroid cancer; early studies are being conducted in prostate cancer)*	November 29, 2012	Small molecule TKI (tyrosine kinase inhibitor), which primarily targets RET kinase, MET (mesenchymal epithelial transition factor), and VEGFR2 (vascular endothelial growth factor receptor 2).
PROSTVAC-VF	Phase III studies planned	Prostate cancer vaccine

PC indicates prostate cancer. Source: US Food and Drug Administration, www.fda.gov.

A. Mark Fendrick, MD

Team-Based Approach

Dr Fendrick asked for comment on the emerging concept of a "team-based" approach to cancer treatment, which encourages greater integration and cooperation among all those involved in a patient's care, including medical oncologists, urologists, radiologists, and even nurse practitioners.

Dr Crawford: We have had a multidisciplinary team in place for several decades.…It is tough to get all of the specialities together, and we do not all agree. Now what we have shown, and this has been shown not only with our group… is that folks who are treated in our multidisciplinary clinic actually have better survival rates than do patients in Colorado who do not. It is not just that selection bias, because we do get some tough cases.…This does make a difference, and men appreciate it.

What sometimes happens, unfortunately, is that if the practice has a robotic machine and everybody needs to get a robotic prostatectomy, you think it is great. If you have IMRT (intensity-modulated radiation therapy) or protons, then that is what you do.…

There are multiple ways people can be treated and you have to be honest with them. Often with early prostate cancers, the cure rate is the same with all of the treatments; there are just different side effects. When people exaggerate the lack of side effects, that leads to some of the controversy that exists right now in prostate cancer.

Dr Fendrick then asked Dan George, MD, to comment specifically on whether the team-based approach was "an outlier or the norm."

Dr George: I think this is becoming more and more the expectation for patients. This goes beyond prostate cancer. If you look at cancer in general more and more of our therapeutic modalities; from pancreatic cancer, rectal cancer, or esophageal cancer… (we are moving toward) the multidisciplinary approach. There is a growing expectation for cancer patients that they are going to be cared for by a team, it is not a single-doctor management plan any more.… As Dr Crawford said, it is hard to get everybody together. One of the big advantages we have in academic medical centers is the opportunity under 1 roof to have shared clinics and shared infrastructures, so that with 1 visit patients can see multiple specialists.…

It is our credibility as care providers for this patient new to cancer to know that he is getting the best choice based upon all of the options presented, and that he is not just hearing a biased presentation on how he should be managed.

As you have heard, with screening we are going to have patients who do not need treatment at all, or need minimal, single modality treatments; those patients with more locally advanced cancer are really going to need a multi-modality approach to management and treatment. For patients to really understand and accept where they are in that spectrum we have to have credibility. For most educated cancer patients, this is now the expectation. And I think you will see the community doctors more and more finding ways to provide that in their environment.

E. David Crawford, MD

Shared Decision Making in Selecting Treatment Options

Dr Fendrick next asked for comments about benefits of shared decision making, in which the patient is engaged in the discussion of which treatment choice makes sense for his particular cancer. Despite a more patient-centered approach in academic centers or large practices, he said that AJMC tends to receive papers that illuminate Dr Crawford's observation: if a prostate cancer patient sees a radiation oncologist, he is more likely to receive radiation therapy; if he sees a surgeon, he is more likely to end up having surgery. Do large groups tend to realize early on that a given patient may benefit from particular type of care? Dr Shore responded first.

Dr Shore: Historically, we have practiced in silos in the community, but what we are seeing now is the aggregation of large groups, particularly in medical oncology and urology communities. Large group practices—which are probably defined as anything more than 10 physicians—afford a level of subspecialization.…I am seeing more large urology groups, as well as medical oncology groups, hire radiation oncologists and hire urologists within a medical oncology group and vice versa.…

Getting back to the decision regarding the patient's best treatment choice: I would hope that this would prevent that patient from just getting siloed into having his prostate removed, or being radiated if he only

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saw the physician who only offered that 1 form of therapy. I think throughout all of medicine we have recognized that we have to do a better job of making sure all options are explained to patients.…

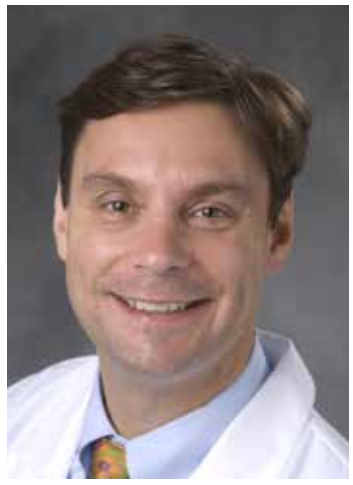
Both in academia and in the community, we have not paid enough attention to outcome data and quality measures. We are really starting to see that now; and from a payer's standpoint that has huge implications. We have a finite amount of resources to allocate to these therapies.

Dr Crawford: One of the challenges that I see, and this is actually being commented on by the Office of the Inspector General, is that a group gets an IMRT machine and all of a sudden the reimbursements are terrific for that.... The number of cases they refer internally for IMRT goes up, and other things go down. What are your comments on that?

Dr Shore: Perhaps you are alluding to a recent report by the (Government Accounting Office) GAO, but (that report was) lambasted because the results were not evidence-based.…We certainly can do a better job of policing outliers; those in our subspecialties and specialities who are not following best practices.… There is no doubt we have outliers, every profession does; historically we have not done a good job (of policing them) but I think we are recognizing the importance of doing so. But the in-office ancillary exception is vital as far as I am concerned, absolutely vital, to the future of the independent practice of medicine. There are those who would take the outliers and use that across the board and take away physicians' abilities to have an integrated facility. That I think would be incredibly detrimental in the long run for the future of independent practices of medicine.

Dr Fendrick asked the other panelists to respond, and to discuss what tools are used to ensure shared decision making, to ensure that prostate cancer patients get an unbiased description of their treatment options.

Dr George: I think we are recognizing that there are different ways of presenting this information, and we are becoming a little bit more sophisticated in doing this.…In an ideal world you do not need a multidisciplinary clinic. In an ideal world any one of us as prostate cancer providers ought to be able to equally represent the other choices, the other modalities and approaches. But to Dr Crawford's point, that is not the world we live in; we all have biases whether we admit them or not. A multidisciplinary clinic allows us to balance those out. A benefit of a multidisciplinary clinic is that it regrounds us on the data from these other fields, and in tools like this to understand how best to present treatment choices to patients. Once you start practicing this way, it affects how I talk to patients in my own clinic when I am seeing them as the only cancer specialist.…



Daniel J. George, MD

Dr Crawford: I would agree and disagree when we talk about multidisciplinary clinics. You cannot expect me to know what a medical oncologist knows; you cannot expect a medical oncologist to know what I know. I think the benefit of a multidisciplinary clinic is that it starts out with pathology. I am not a pathologist, but we will see 1 or 2 patients a month who were advertised as having prostate cancer, but do not have prostate cancer; instead they have ASAP (atypical small acinar proliferation) or PIN (prostatic intraepitheial neoplesia).…The pathologist is important here; the radiologist is also important in picking up lesions and things like that; the medical oncologist can talk about trials and outcomes.

I think that Dr George is right, we all have a knowledge of a little bit about radiation, but it is not perfect.

Dr Fendrick agreed with their points, and then asked, based on unmet needs and challenges, where research and development efforts should be aimed.

Dr Shore: We have this odd spectrum of aggressive to indolent disease in prostate cancer, as opposed to many other solid tumors that tend to be more uniformly aggressive. How do we decide who the men are in the 50 to 60% of newly diagnosed cases that need aggressive treatment? How do we best treat them? That's where we have to have the multidisciplinary philosophy that we just discussed.…

In addition, we are now entering new metrics. The metrics we have historically used to decide on aggressiveness of therapy have been age and actuarial survival comorbidities; specific to prostate cancer, we have looked at histopathology, the Gleason Score, and the stage of the disease—which mostly involves the digital rectal exam and PSA. Now we are looking at genomic assays and other biomarkers to help us decide additional testing or aggressiveness of therapy.

We really are now entering into a new world, and I think it is incumbent upon not just urologists and medical oncologist, but also primary care physicians to understand that we can do a much better job in selecting patients who require more aggressive therapy. We still have patients who, if we fail to do appropriate targeted screening, then we will miss further opportunities to help the men who need aggressive therapy early on.

Dr George: I agree 100%. I think that is our biggest risk—that we make a blanket decision not to screen. I think there are a lot of people in primary care who have already come to that conclusion, and their patients are going to suffer.

We are not reflexively treating everybody with surgery or radiation therapy, and there are growing numbers of patients with active surveillance, which is affording us to be aggressive in treating the patients who need it.

Dr Fendrick: I completely agree, and I think ultimately the idea of targeted screening will not just be used in prostate cancer screening, but will be used other screenings as well. We have seen advances in human papilloma virus (HPV), and now our cervical cancer screening rates have changed. Obviously, you all know of the great controversy in breast cancer screening—when to start and how often.

Disparities in Screening and in Treatment

Dr Fendrick asked whether the new treatments and diagnostic tools available for prostate cancer, which can invite a more targeted approach, are cause for optimism, or whether treatment gaps—and differences in mortality—existed for certain groups.

Dr Crawford *clarified that there have always been calls for more focused attention to high-risk groups, including African American men and those who were exposed to Agent Orange in Vietnam. "This is not new; this has been around for a while but people have just not paid attention." Conversely, no professional society endorsed practices like PSA tests for elderly men on oxygen, and yet those things happened. What's happening now is that efforts by the American Cancer Society and USPSTF are forcing physicians to adhere to long-standing best practices. Dr Shore responded.*

Dr Shore: There are some great advances though, and there are still some additional low-hanging fruit. Dr Crawford mentioned the challenge with the African American community. If you look at all of the up-to-date most recent American Cancer Society statistics the disparity and mortality for prostate cancer… there is virtually upwards of a 100% differential in mortality through much of the southeast of the United States and in urban areas. It speaks to receiving inadequate care, inadequate screening, inadequate treatment, and that is real low-hanging fruit to do away with that disparity.

Dr Fendrick asked whether the disparities were due to a more aggressive disease at diagnosis, or whether these differences played out regardless of how advanced the disease was at diagnosis.

Dr Shore: It is a great question. It is multifactorial, and it is potentially an earlier, more aggressive disease for some. It is being diagnosed too late for many. It is receiving inadequate therapy for many, both in localized as well as in advanced disease. This allows us to segue into the burgeoning advancements of advanced prostate cancer therapies. Obviously we are thrilled over (this), for advanced prostate cancer is clearly one of the best examples of tremendous advancement from preclinical to clinical or from bench to bedside, where we are doing a markedly better job in keeping men alive and maintaining quality of life. Among African American men, many of them have not been brought into the trials that have shown these advancements and still are not receiving therapy. In my own state of South Carolina, Medicaid lags behind in offering advanced therapies to patients who could benefit from FDA-approved therapies. It is a multifactorial issue for certain populations, no doubt.

Excitement Over Emerging Agents

Dr Fendrick asked about coverage for new therapies, such as abiraterone and enzalutamide, and invited panelists to comment on clinical data on emerging agents.

Dr Crawford: In the last 3 to 4 years there have been 7 new drugs that have been introduced in the arena of advanced prostate cancer, with more to come. There was a dearth of activity for decades; we had LHRH (luteinizing hormone-releasing hormone) antagonists, and we had mitoxantrone, and we have other types of chemotherapy with taxotere. Now we have these new drugs and the interesting thing is all of these drugs are different. They are immunotherapy, they are new chemo, they are anti-androgens, LHRH antagonists; they are radionucleotide, bone preserving agents. It is an exciting time (**Table**).

Dr Crawford then asked Dr George to comment on how all these new drugs are inte-

grated. Are they sequenced? Are they used together? And Dr Crawford raised the issue of cost, as many cost up to $100,000 per year.

Dr George: You bring up all of the critical issues in 1 question—it is a little daunting. This is a time of excitement, and a little bit of anxiety as we see a sudden explosion of treatment options all at once. And the reason that is a challenge is that they are developed largely in parallel, so we do not necessarily have the data of using these agents in sequence or in combination.

Dr George explained having 7 new therapies at once, with relatively few data on how they should be used in sequence or in combination, presents challenges for practitioners. Which patients need which therapies? He noted several points: (1) Most of the new therapies are based on overall survival (OS) improvement. (2) These therapies work through different mechanisms— these are not "me, too" drugs. Immunotherapy, for example, is in a class by itself. He continued:

Dr George: It really is a fantastic opportunity, but it is a real challenge to understand: do these disparate mechanisms actually add to each other in sequence? What is that sequence, and are they overlapping when you block the testosterone pathway with an androgen-synthesis inhibitor, such as abiraterone? Does that somewhat negate the benefits of subsequent enzalutamide, or vice versa? I think those are some of the challenges that we face right now, which I think payers are going to face, in helping us justify the sequence that we do.

Dr Fendrick noted that previously, medicine did not worry about cost-effectiveness until there was a well-known and rigorously established benefit. Having so many new drugs at once makes that impossible.

Dr Fendrick: Dr George, you mentioned the melanoma example; this is not dissimilar to a discussion we had recently where the enthusiasm was high, the science was fascinating, but at the same time while the potential was clear, there wasn't a lot of clinical experience using these drugs in sequence or in combination—even though the theory would suggest that they would work better together than alone.

Dr George: We do have some sequence data; it is not obviously complete, but we do have some. For instance, the immunotherapy sipuleucel-T was largely given to a patient population that had not received chemotherapy. Eighty-five percent of the patients had never received chemotherapy for prostate and showed a significant survival advantage in that population. Incidentally, that percentage improvement in survival looked similar in the 15% that did receive chemotherapy. So, it looks like you could give that therapy either before or after chemotherapy, but the strongest data is giving it before chemotherapy.

Among our secondary hormonal therapies, abiraterone acetate, which is an androgen-synthesis inhibitor, and enzalutamide, which is an androgen-receptor antagonist, have both shown significant improvement in survival in patients that had received prior chemotherapy. This suggests that chemotherapy is not selecting out resistance for those strategies. Abiraterone has also gone on to show a significant clinical benefit to a broader patient population, those patients who had never received chemotherapy.

I should point out that in prostate cancer, only about half of the patients ever go on to receive docetaxel-based chemotherapy or other chemotherapies, so when we look at a post chemotherapy patient population we are looking at a relatively narrow field of patients, who are somewhat healthier but more aggressively treated. When we look at a pre-chemotherapy population of patients, we are looking at a much broader cross section of the population of castration-resistant prostate cancer (CRPC) patients.

There, too, abiraterone showed significant clinical benefit. This was not necessarily a statistically significant improvement in OS because the study was stopped short of that end point, but for all of the clinical end points before that—disease progression, time to chemotherapy, pain, and other deterioration in performance status—all strongly favored abiraterone over prednisone alone. This is suggesting, again, we are changing the natural history of this disease by using a drug like that early….

Neal Shore, MD

The Challenge of Personalized Medicine

Dr Fendrick asked the panelists to address how clinicians and payers can deal with the "moving target," the challenge of matching the appropriate treatments to the right patients with limited data.

Dr Crawford responded by saying it was time to think "outside the box." For years there very few treatments, and the discussions were along the lines of "pain or no pain." Dr Crawford highlighted how the discussion of treatment costs has shifted; years ago, he was an author on a paper in the New England Journal of Medicine *about men paying $240 a month to extend survival by 6 months, and that was considered expensive. Today, he said, instead of $240 the costs are "tens of thousands" of dollars a month.*

Dr Crawford: Is there a rationale for using some of these new agents, the C17-20 hydroxylase agents, such as abiraterone, early? Maybe, as there was a study that was just done that will have some results. Should you do that early, should you use an antiandrogen receptor different from casodex and other ones? There is a rationale for combining abiraterone with enzalutamide. So, in the real world, I would say okay, we can study this all, but is it going to take 15 years?

Dr Crawford says years ago, leukemia researchers were criticized for going from a single drug to 3 or 4 to obtain data, but that may be the way to convert prostate cancer into a chronic disease, rather than a fatal one. Giving a patient sipuleucel-T will not react with other treatments, for example.

Dr Fendrick responded that this approach reveals the challenges with so many therapies: "The more we get and take advantage of this personalized medicine the harder it is…to educate the payer community on this idea.… This is about trying to get the right agent or the right treatment to the right patient at the right time."

He asked Dr Shore to discuss whether guidelines from the National Comprehensive Cancer Network (NCCN) are keeping pace with cutting-edge science. "It seems from the operational standpoint to be really challenging."

Dr Shore: Organizations such as the NCCN, which do have CRPC Guidelines based upon their panel of key opinion leaders, do try to give guidance to urologists, medical oncologists, and radiation oncologists on how to best deal with these newly approved, very exciting, highly individually unique mechanism of action therapies—which also have price tags.

Also, we recently saw publication of the American Urological Association CRPC Guidelines, and they described 6 different index cases starting from the patients who are CRPC rising PSA, with a castration level of testosterone and no radiographic evidence of disease and asymptomatic, to the patients who are at the very end who are after chemotherapy who are progressing as well. It is a very nice breakdown, and of course since its publication in May 2013, right afterward we already had the approval of Xofigo or Radium-223. This speaks to what was said earlier, where we are continuing to develop new therapies to add to our armamentarium, which adds to the confusion on how to sequence combinatorial strategies.

This can potentially create confusion from the payer's side as to when they should be providing reimbursement. The bottom line is there are now very well described recommendations by the AUA CRPC Guidelines Committee, as well as the NCCN on what the Level One Evidence is and what is less than Level One Evidence for making decisions.

In my mind, the best methodology right now from a payer's standpoint to say, OK, we understand the FDA-Labeled Indication and therefore we should respect the labeled indication and where they fit in to those 2 discrete guidelines. I think as long as we follow that, then we are not going to have clinicians and patients be disappointed that they do not get adequately supported by their payer.

Dr George: I agree, but there is a limitation; and I appreciate that the guidelines just did not reproduce themselves. I thought the AUA did a really nice job of doing something different from NCCN. As much as I respect the NCCN guidelines they are not helpful to clinicians, because all they do is recapitulate the level 1 evidence we have and then the level 2 evidence is basically just consensus building….I think what the AUA put together is much more contextual and helpful in helping clinicians say, "Oh, my patient looks like this scenario or that scenario, and I am going to follow that approach."

Dr George explained it is one thing to tell practitioners when to start a therapy; it is quite another to tell them to stop, or when to switch. In this area, there is very little guidance.

Dr George: The payers cannot say anything there, because there are no data one way or the other. Once they have paid for a medicine they are not going to stop paying for it, so there is no pressure on that side, either.

Offering Guidance for Payers

Dr Fendrick said that precedents exist for payers in other chronic conditions, such as hepatitis C, in which if markers do not respond treatment is stopped. He encouraged each panelist to offer advice to payers on how to decide what to cover in the new world of prostate cancer treatment, and laid out the extremes:

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Dr Fendrick: Clearly we cannot give every drug every time to anyone. Nor do we want to get to a situation where you are going to have to call us for a prior authorization every single time.

Dr Crawford said he disagreed somewhat with Dr Shore about the value of NCCN guidelines, and to an extent with the AUA guides. The issue, as he sees it, is not whether there is a guide for one drug following another, but that the guides do not address "what I think we all believe is the bright future." Cures may be possible where they were once not.

Dr Crawford: We need to think outside the box and take some chances. The chances we are taking to test this cancer, and putting together bleomycin and cisplatin when these were monotherapies, and then people did doublets and triplets....Well, I think we have to do that in prostate cancer.

Yes, it is going to be extremely expensive; it could be $400,000 a year, but we have the American ingenuity and the wherewithal that we will find better ways to do it, or there will be other drugs that come along that are less expensive in the same category.

I think we really owe that to men with advanced prostate cancer, to make that step and start doing this and seeing how it goes.

Dr George: I would echo that. There is a very important point here, and that is that we cannot be complacent with prostate cancer....We have not cured anybody with this disease, and even patients who go through all of these therapies; I have plenty of patients who have gone through all of them and they are still dying of prostate cancer, and they could still benefit from additional treatments.

This is a research question, and the national research agenda of our cooperative groups, of our industry, of the federal government or the US Department of Defense, needs to get behind those kinds of initiatives for sure, and maybe the payers do, too.

Dr George agreed that practitioners need better predictive markers to match treatments with patients, as well as more guidance on when to stop or switch therapy. The PSA, he said, is a "pretty good marker of response to those agents that are targeting the testosterone and androgen-receptor pathways, but it is not perfect."

Dr George: I think there is a blend here of continuing to do the envelope-pushing combination strategies, with cost to the wind—let's try to cure the disease—because that is going to be the most cost-effective manner of managing these patients in the long run.

Dr Shore: I would like to respond to the 2 of you disagreeing with me. I think when you say "real world" that really is interesting to me, because 80 to 85% of cancer is practiced in the community, not in academic centers.

The real world is fighting to get patients reimbursement for these expensive newly approved therapies. I am in those trenches and I see how that happens, but I am not sure that in the academic centers you see it to the same degree. Perhaps you do, but in the community you really come to it in a more direct way. And so the question that I was asked was, "What are guidelines for payers?" or "Are there guidelines for payers?"

It is a law that if there is a level 2 recommendation by NCCN, then the (Centers for Medicare & Medicaid Services) has to reimburse. So, for the payer population that is going to be hearing this, that is very important. It is a separate issue to think about and to discuss issues of predictor response, and resistance, combinatorial, and sequencing strategies.

The question that was asked is, "How are we going to pay for this, and what would be the recommendation to the payers regarding these new novel and newly approved therapies?" and, "Where do they best fit in based upon the guidelines?" When NCCN gives something a level 2, by law CMS has to pay for it, so that actually is federal policy. That I think was the point I was trying to make.

Dr Fendrick: I want to thank all of you for this really robust conversation on not only where we are, but where we are going and where we need to push the envelope on prostate cancer. **EBO**

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PEER EXCHANGE Immunotherapy

Immunotherapy in Cancer Care: Understanding the Impact of Shifting Treatment Paradigms in the Managed Care Setting

The American Journal of Managed Care convened an expert panel to address the impact of increased use of immunotherapy in treating cancer in a managed care setting. According to the American Cancer Society, immunotherapy is a treatment that wards off disease either by boosting the immune system in general or by training it to attack specific cancer cells. Immunotherapy may be used alone or in combination with standard chemotherapy regimens.

Panelists discussed the positive and negative aspects of using immunotherapy, traditional chemotherapy, and combination regimens. They addressed the importance of promoting both patient and provider understanding of immunotherapy. Finally, panelists discussed the cost associated with immunotherapy in cancer care.

The discussion was moderated by **Peter Salgo, MD,** a professor of medicine and anesthesiology at Columbia University and an associate director of surgical intensive care at NewYork-Presbyterian Hospital, New York City. The panelists included:

- Jeffrey Weber, MD, PhD, senior member of the H. Lee Moffitt Cancer Center and director, Donald A. Adam Comprehensive Melanoma Research Center, Tampa, Florida.
- Michael A. Kolodziej, MD, national medical director, Oncology Solutions, Aetna, Inc.
- Daniel J. George, MD, Duke Cancer Institute.

Peter Salgo, MD, initiated the discussion by stating that immunotherapy markets were expected to exceed $14 billion this year; of the 12 FDA (US Food and Drug Administration)-approved drugs in 2012, 11 cost more than $100,000 a year. He said this points to a trend toward increasing costs for everyone. Dr Salgo then specifically asked Daniel George, MD, to comment on the previously unmet medical needs that are now being met by cancer immunotherapies.

Daniel J. George, MD: Cancer immunotherapy, and immunotherapy in general, has a long history of almost 100 years or more of recognizing the importance of the immune system in monitoring, preventing, and controlling cancer. We probably have not used this to our best advantage, but recently there's been a breakthrough in a number of agents and strategies that have harnessed this access of therapy, an endogenous approach to managing this disease and taking advantage of our own immune system and the way it fights cancer.

Dr Salgo: The way I've looked at it, if I may, is in the past when you gave chemotherapy, you just killed all the cells and hoped that the rapidly dividing cells went first and then salvaged patients back. That's not what's going on.

Dr George: This is a really different paradigm. The immune system is present and we are trying to manipulate it in a way to reactivate it against cancer. There's a concept called tolerance where, by multiple different strategies, cancer cells can evade recognition by the immune

system; there's a way of reharnessing the immune system by overcoming that tolerance. Unlike chemotherapy or radiation therapy, where the treatment stops when you stop the drug, these are therapies that potentially could keep going and keep working following reactivation. We're actually sort of vaccinating, if you permit me to use an umbrella term that may be imprecise, against cancer such that you are sensitizing an immune system against a particular tumor. You don't have to re-vaccinate every 3 days. You give it once and the immune system keeps working.

Jeffrey Weber, MD, PhD: Well, the Holy Grail of cancer immunology is to create a cancer vaccine. Provenge was the first and only cancer vaccine that was ever approved. But that is truly the mantra, that is, the immune system is the ultimate way to perform targeted therapy. So immunotherapy is targeted therapy, and its hallmark is memory.


Jeffrey Weber, MD, PhD

Michael A. Kolodziej, MD: I was a practicing oncologist until just recently, and there's an unmet need because what we were doing wasn't working very well. So now we have the emergence of immunotherapy as an approach. We have the emergence of targeted therapy and even to the point of precision medicine as an approach, and we'll see what wins. It's very exciting because the science has advanced quite rapidly, but what we did earlier wasn't very effective in most patients.

Dr Salgo continued the discussion by asking the panelists to clarify his understanding of the mechanism by which immune therapy works. His understanding was that we continually develop malignant cells every day that are consumed by the immune system to prevent tumor development, and the immunotherapy drugs seem to target the failure of immune recognition and immune response.

Dr Weber: There are certainly data to suggest that this idea of immune surveillance is indeed valid. On the other hand, people on immunosuppressants don't always present with 30 different types of solid tumors. Transplant patients often develop squamous skin cancers, especially virally related squamous skin cancers. So there are data to suggest that we always have immune surveillance to prevent cancer from developing.

In response, Dr Salgo queried the panelists on the different types of immunotherapy drugs that are now available and the types of cancers they treat. In their expert opinion, which of the available treatments could be considered clinical successes with a meaningful impact on patient outcomes?

Dr Weber: You can divide immunotherapies into 4 or 5 categories: these include chemicals like cytokines; antibodies… cells, which are not really well developed; vaccines, which is always the Holy Grail to try to vaccinate someone against his or her own cancer. You've got 1 approved vaccine. One of the antibodies, which are the most exciting and promising, is approved. That's ipilimumab, the anti-CTLA4 antibody. In terms of the cytokines, in 1996 and 1998 IL-2, interleukin-2, was approved for kidney cancer and for melanoma. The cell therapy is immature, and you will hear a lot more about the antibodies coming up in the next couple of years.

Dr George: I know we're all very excited about the newest approvals and directions of immunotherapy, but just to take a look back, we've made tremendous progress with immunotherapy over the last 30 years. Bladder cancer is the tumor we use immunotherapy in the most on a regular basis, with bacillus Calmette-Guerin (BCG) in instillations for superficial bladder cancer, which has changed the natural history of superficial bladder cancer. How does IL-2, which has been around a long time, recognize that this is a mechanism that, although rare, does result in complete responses? These are durable complete responses in some tumors, some advanced metastatic solid tumors, and in renal cell and melanoma, in particular?

With some of the newer approaches, however, we're seeing even a broader range of tumors that are susceptible to these strategies and we'll talk about some of those examples as we get into the drugs. But to me, this is one of the most exciting areas right now and the validation is that we're seeing this not in the niche of one tumor or another but beginning to branch out into a whole host of different tumors in stages.

Dr Weber: Immunotherapy never got respect because it was always that drug which worked in 1 or 2 cancers like melanoma or kidney cancer, which were the immunotherapeutically sensitive histologies. But now, PD-1 has definite activity against non-small cell lung cancer. So, now, for the first time, the common epithelial malignancies will have immunotherapeutic options and that's great.


Peter Salgo, MD

To follow up, Dr Salgo asked Dr Kolodziej and Dr George to comment on the restrictions if any that are placed on reimbursement for these agents.

Dr Kolodziej: I think from a payer perspective, the science aside, there's not a great distinction around mechanism of action or promising early results. It's all about results. And I think managed care has a historical way of dealing with new therapies that are expensive, and the most typical is prior authorization or precertification. If you look at the new drugs, and you mentioned it in your prologue, they're all very expensive. And then we have a lot of discussion about how we should add expensive drug A to expensive drug B. You don't see a new drug that didn't come out at $10,000 a month, but I don't really know how that number is arrived at.

However, there is an established way of dealing with the process, and that continues to be the way of dealing with it, and that is prior authorization or precertification. And I will say that the prior authorization and precertification clearly reflects the FDA label. If you're going to get Provenge, you have to be minimally symptomatic. And, if you call us to get it approved, we will ask you that question.

Dr George: I think this is a good point on the FDA labels. This will gain increasing importance; you are seeing real trends for our immunotherapies now that are expensive, and people really are following these labels. These really do matter. In years past, they were just sort of an entree into the field and then people did a lot of off-label use of treatment. We see much, much less of that because of the expense, which in some ways is appropriate; we should be a data-driven field.

Dr Weber: Although, to tell you the truth, the data that we have access to are not always what is reflected in the package insert or the label. An example would be, reinduction therapy was part of the original trial that led to the registration of ipilimumab. Admittedly, a modest number of patients on those registration trials were reinduced. Over time, the reinduction rate, if you get ipilimumab, if you're stable and respond over 24 weeks, maintain it for some modest period of time, and then relapse later, which is most patients, that you can be reinduced and have about a 40% response rate, which is very respectable by anybody's standards. That's not in the label, those of us who know would want to reinduce, but that doesn't mean we'll always get to be able to do it. I mean, I can argue my way pretty well with most insurers to get it done, but most community doctors won't.

Dr Salgo steered the conversation to talk about the guidelines published by the NCCN and CMS. Dr Salgo sought the panelists views on the increased paperwork and requirements, whether they thought it a good thing or simply bureaucratic obstructions.

Dr Kolodziej: I think you will find fairly consistently that most payers, national payers, largely respect what the NCCN has to say almost completely. Most payers realize they do not have the expertise in-house to try to adjudicate the quality of the evidence, and they look to a panel of experts to help them negotiate those waters, which is fair. The radiation therapists are not all happy with NCCN. They think that protons guidelines are not up-to-date. Maybe the immunotherapists aren't happy with the immunotherapy, although they do say you can give ipilimumab a second time in the NCCN guideline.

Dr Salgo: What I'm really trying to get at here is, guidelines are fine. And what I hear you saying is guidelines are guidelines and they do make sense, and experts have approved them and signed off on them. But on top of these guidelines, there's more paperwork, and more sign-offs, and more gatekeepers. Is this rational or is it simply a way for payers not to pay?

Dr Kolodziej: I personally believe the answer is we're going to get to a point in healthcare reform, this is not Aetna's view, this is my view, where we go from a point where the payers are the gatekeepers to where providers become gatekeepers. And so I think that the burden of adjudication of appropriateness of evidence is going to shift. That locus of control is going to shift to providers. Now, providers may or may not like that.

Dr Weber: But the providers will need help, which is why pathways and other ways of treating patients are going to become paramount for oncologists, which means it will take away our autonomy.

Dr Salgo specifically wanted to know whether the increased bureaucracy and paperwork, over and above the scientific, CMS, and NCCN guidelines, would force the providers into giving up.

Dr Kolodziej: No, I don't think so. When I started (at Aetna), I reviewed every single prior authorization policy we had at Aetna. And if you can't finish that form in 1 minute, you've got a problem. I get administrative burden. I was in practice for a long time, and I worked for US Oncology so I know a lot about administrative burden, and the burden is small. The truth of the matter is: give me a solution. Tell me what else we ought to do, and the answer is, we trust the providers. The idea that they're motivated by profit, I don't buy into that.


Michael A. Kolodziej, MD

Dr George: And I would agree with Dr Kolodziej on this one. I don't see this as a burden. Filling out the form is not the problem, but when we get the largely inappropriate peer-to-peer, that's an annoying burden that we sometimes have to carry. ... If a request for coverage gets denied, then we have to request a peer-to-peer, doctor-to-doctor, or healthcare-professional-to-healthcare-professional review of the case. We take time to set that up and then review the case. It's frequently because some of the records were either not available or there was a misinterpretation of the case. It's usually clarified, but it just takes time. This makes us stop and think whether this really is appropriate use of therapy, and very expensive therapy at that. Going forward, we may need to pause and think about cost as well.

Dr Salgo: From a payer perspective then, which has more value? You can define value any way you like. Is it immunotherapy or genomic precision therapy?

Dr Kolodziej: I've actually been thinking about it a long time. And I don't mean to trivialize this, but there are different ways to get at the problem. They're both intellectually satisfying. I'm not sure there's a huge cost differential between them. We will find out. The data will tell us what the right approach is.

Dr George: Are they mutually exclusive?

Dr Kolodziej: I think not.

Dr Salgo: However, they had the cost additive?

Dr Kolodziej: Maybe yes and maybe no. So I think it's a mistake, and I felt this way for a very long time, to focus solely on what the cost of the infusion is. I think we need to think about other things when we think about the cost of care of a cancer patient. If you look at the cost of an episode of care for a cancer patient, about 25% is the chemotherapy, but another 20% is imaging, another 30% is hospitalization. All I'm saying to you is this, if the Institute of Medicine is right, 30% of healthcare is wasteful.

As we get into a world of precision therapy, the opportunities for improving care and controlling cost is not keeping the right drug from the right patient, keeping the patient out of the hospital, keeping them out of the ED, dealing with their symptoms at home, knowing when to say when. And I can't stress that last point enough. This is again my opinion, not Aetna's, but the greatest return of investment (ROI), and this is from work we did with US Oncology, is really on end-of-life care and doing the right things at end of life.

Dr Salgo brought up the encapsualization of care. The cost of immunotherapy is known up front, because it keeps working with a single administration. Whereas, with traditional chemotherapy, you're going to be paying out of pocket.

Dr Kolodziej: No one is saying this is curative therapy yet. Let's just recognize that there's an episode of immunotherapy treatment and we don't know how long that episode is going to (require coverage).

Dr Weber: But let's hold that thought for a second because as data develop with the use of ipilimumab, at least in melanoma, there has been or there is a plateau of survival in patients who are out 3, 4, or 5 years. So, if 18% of your patients are alive at year 3, 18 or 19 at 4 and 5, some of those patients are probably cured. And the best data from the longest follow-up at 7 and 8 years suggested if you have a complete response (CR) or a near complete response, made CR by surgery with ipilimumab in melanoma, you're going to be alive continuously in remission at least 90% of the time, out at 7 or 8 years. So maybe those patients are cured.

Dr Salgo: I want to put this on the table without comment. One of the very few times I've heard the word "cure" in this context, whether or not we can use it reliably, the fact that we're even discussing it is remarkable.

Dr Weber: The fact that in current targeted trials, for example, with BRAF, BRAF/MEK drugs in melanoma, we're seeing patients on protocol and they come in and you look at the chart. It's week 140, week 170, week 180, which is phenomenal.

The ultimate outcome is survival. If I were a cancer patient and I had treatments pitched to me by my oncologist, my first question would be, 'How long am I going to live compared with not having treatment or compared with the control treatment and how am I going to feel?' So it would essentially be the quality adjusted years of life prolonged, which is not a trivial calculation. The problem is in the medical oncology business, at least until recently, we haven't been able to quantitatively assess what that benefit would be. Now we have more data, and I would agree with what Dr Kolodziej said, about 30% of everything we do is wasted. I've been saying that since I became an oncologist 25 years ago, and I was absolutely convinced that at least a third of what I did was a complete waste of time. That's got to change.

Dr George: I think the new healthcare reforms should give us more opportunity to have a say in that. I think the challenge is that now we're going to own that more and that's going to come back to us in terms of a reimbursement model. And that's something we are inexperienced in.

Dr Kolodziej: I think the interesting thing is that we have been stuck for a very long time in a paradigm of designing clinical trials with a view toward what registration for that drug should look like. That is going to change because now there's going to be a burden on the innovators to look at meaningful outcomes that will allow them to position their product, immunotherapy product, or targeted agent, to position it in a global treatment for that patient. So it shifts the burden of identifying value, and as a healthcare consumer I'm all for that.

Dr Salgo then asked Dr George to comment on the newly approved mover-and-shaker drugs in literature.

Dr George: I'll simply walk through the clinical data and the mechanism of action of these drugs. Provenge is an autologous cellular immunotherapy from the patient's own cells. It's really the ultimate in personalized therapy. The drug is made from the person's own cells through a process called leukapheresis; the cells are then shipped to a centralized laboratory and activated ex vivo against antigens that are relevant to prostate cancer, in this case, a fusion protein, a prostatic acid phosphatase in GMCSF (granulocyte macrophage colony-stimulating factor), an immunostimulant. That creates, within that peripheral blood mononuclear cell compartment, some activated cells against those proteins, which are then reinfused back in 3 days later, almost like a blood transfusion for the patient, an autologous blood transfusion. It's repeated every 2 weeks for 3 doses. So it's a 0-, 2-, and 4-week regimen.

Of 2 independent clinical trials, a relatively small randomized study demonstrated an overall survival advantage of about 4 months and a second pivotal trial, 512 patients randomized, demonstrated about a 4.1 month improvement in overall median survival with a hazard ratio of about 0.77. And interestingly, as alluded to by Dr Weber, the patients that live longer derive a greater benefit. So a landmark analysis at 1 year demonstrates about a 12% improvement in survival, about a 24% improvement in overall survival by 2 years, while patients that are out to 3 years, there's a 32% improvement in overall survival for that population, showing an absolute benefit that's much greater. Bottom line, identifying the patients who are destined to live 3 years is ideal to treating with Provenge.

Dr Salgo: And, again, with just 3 doses, you know up front what it's going to cost.

Dr George: But the benefit is extended over the lifetime of that patient. It's not $100,000 for 1 month. It's an investment in a patient that we believe is going to live 3 years or more. If you annualize that out, it's $30,000 a year.

I don't want to make it sound like it's a black and white thing. This is against 1 antigen that may or may not be relevant, and some or many of these patients may not necessarily fully respond to that. I view this more like a platform. Because it has very low toxicity, there really isn't a long-term residual toxicity from this treatment, in addition to the opportunity to building on this with subsequent therapies, whether targeted, immunologic, or otherwise. We'd now like to build and improve on this therapy.

(continued on SP44)

NOW APPROVED

FOR PREVIOUSLY TREATED MCL

imbruvica™

(ibrutinib) 140mg capsules

INDICATION - IMBRUVICA™ (ibrutinib) is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is based on overall response rate. An improvement in survival or disease-related symptoms has not been established.

Learn more at www.IMBRUVICA.com

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - 5% of patients with MCL had ≥ Grade 3 bleeding events (subdural hematoma, gastrointestinal bleeding, and hematuria). Bleeding events including bruising of any grade occurred in 48% of patients with MCL treated with 560 mg daily. The mechanism for the bleeding events is not well understood. Consider the benefit-risk of ibrutinib in patients requiring antiplatelet or anticoagulant therapies and the benefit-risk of withholding ibrutinib 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. At least 25% of patients with MCL had infections ≥ Grade 3, according to NCI Common Terminology Criteria for Adverse Events (CTCAE). Monitor patients for fever and infections and evaluate promptly.

Myelosuppression - Treatment-emergent Grade 3 or 4 cytopenias were reported in 41% of patients. These included neutropenia (29%), thrombocytopenia (17%) and anemia (9%). Monitor complete blood counts monthly.

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

Renal Toxicity - Fatal and serious cases of renal failure have occurred. Treatment-emergent increases in creatinine levels up to 1.5 times the upper limit of normal occurred in 67% of patients and from 1.5 to 3 times the upper limit of normal in 9% of patients. Periodically monitor creatinine levels. Maintain hydration.

Second Primary Malignancies - Other malignancies (5%) have occurred in patients with MCL who have been treated with IMBRUVICA™, including skin cancers (4%) and other carcinomas (1%).

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

ADVERSE REACTIONS - The most commonly occurring adverse reactions (≥ 20%) in the clinical trial were thrombocytopenia*, diarrhea (51%), neutropenia*, anemia*, fatigue (41%), musculoskeletal pain (37%), peripheral edema (35%), upper respiratory tract infection (34%), nausea (31%), bruising (30%), dyspnea (27%), constipation (25%), rash (25%), abdominal pain (24%), vomiting (23%) and decreased appetite (21%).

*Treatment-emergent decreases (all grades) of platelets (57%), neutrophils (47%) and hemoglobin (41%) were based on laboratory measurements and adverse reactions.

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia (7%), abdominal pain (5%), atrial fibrillation, diarrhea (5%), fatigue (5%), and skin infections (5%). Treatment-emergent Grade 3 or 4 cytopenias were reported in 41% of patients. 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.

DRUG INTERACTIONS

CYP3A Inhibitors - Avoid concomitant administration with strong or moderate inhibitors of CYP3A. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA™ dose.

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

SPECIAL POPULATIONS - **Hepatic Impairment -** Avoid use in patients with baseline hepatic impairment.

11/13 K08BR13037C

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Brief Summary of Prescribing Information for IMBRUVICA™ (ibrutinib)

IMBRUVICA™ (ibrutinib) capsules, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

IMBRUVICA is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is based on overall response rate. An improvement in survival or disease-related symptoms has not been established *[see Clinical Studies (14.1) in full Prescribing Information]*.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Five percent of patients with MCL had Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, and hematuria). Overall, bleeding events including bruising of any grade occurred in 48% of patients with MCL treated with 560 mg daily.

The mechanism for the bleeding events is not well understood.

Consider the benefit-risk of ibrutinib in patients requiring antiplatelet or anticoagulant therapies.

Consider the benefit-risk of withholding ibrutinib 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 (14.1) in full Prescribing Information]*.

Infections: Fatal and non-fatal infections have occurred with IMBRUVICA therapy. At least 25% of patients with MCL had infections Grade 3 or greater NCI Common Terminology Criteria for Adverse Events (CTCAE) *[See Adverse Reactions]*. Monitor patients for fever and infections and evaluate promptly.

Myelosuppression: Treatment-emergent Grade 3 or 4 cytopenias were reported in 41% of patients. These included neutropenia (29%), thrombocytopenia (17%) and anemia (9%). Monitor complete blood counts monthly.

Renal Toxicity: Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Treatment-emergent increases in creatinine levels up to 1.5 times the upper limit of normal occurred in 67% of patients and from 1.5 to 3 times the upper limit of normal in 9% of patients. Periodically monitor creatinine levels. Maintain hydration.

Second Primary Malignancies: Other malignancies (5%) have occurred in patients with MCL who have been treated with IMBRUVICA, including skin cancers (4%), and other carcinomas (1%).

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 receiving the ibrutinib dose of 560 mg per day. 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]*
- Myelosuppression *[see Warnings and Precautions]*
- Renal Toxicity *[see Warnings and Precautions]*
- Second Primary Malignancies *[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.

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 TableTables 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.

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 Mantle Cell Lymphoma (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
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 nutritional 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.

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 strong inducers of CYP3A decrease ibrutinib plasma concentrations by approximately 10-fold.

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 administered the dose of 560 mg daily. 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.

Renal Impairment: Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with Creatinine clearance (CLcr) > 25 mL/min. There are no data in patients with severe renal impairment (CLcr < 25 mL/min) or patients on dialysis *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment: Ibrutinib is metabolized in the liver and significant increases in exposure of ibrutinib are expected in patients with hepatic impairment. Patients with serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 3.0 x upper limit of normal (ULN) were excluded from IMBRUVICA clinical trials. There is insufficient data to recommend a dose of IMBRUVICA in patients with baseline hepatic impairment *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Females and Males of Reproductive Potential: Advise women to avoid becoming pregnant while taking IMBRUVICA because IMBRUVICA can cause fetal harm *[see Use in Specific Populations]*.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- *Hemorrhage:*
  Inform patients of the possibility of bleeding, and to report any signs or symptoms (blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions]*.
- *Infections:*
  Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills) suggestive of infection *[see Warnings and Precautions]*.
- *Renal toxicity:*
  Inform patients of the possibility of renal toxicity. Advise patients to maintain adequate hydration *[see Warnings and Precautions]*.
- *Second primary malignancies:*
  Inform patients that other malignancies have occurred in patients with MCL who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions]*.

IMBRUVICA™ (ibrutinib) capsules

- *Embryo-fetal toxicity:*
  Advise women of the potential hazard to a fetus and to avoid becoming pregnant *[see Warnings and Precautions]*.
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day *[see Dosage and Administration (2.1) in full Prescribing Information*].
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose *[see Dosage and Administration (2.5) in full Prescribing Information]*.
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions]*. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions]*.
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists.

Active ingredient made in China.

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

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 Issued: November 2013

K08BR13131B

(continued from SP40)

Dr Salgo: Where does ipilimumab fit in this whole group of pharmaceuticals?

Dr Weber: Well, ipilimumab is a very different drug. Provenge is a vaccine, again, the first cancer vaccine ever approved by the FDA. But ipilimumab is a checkpoint protein inhibitor. The immune cell has multiple brakes and accelerators. If you had a drug that bound the accelerators, you would push the immune system. It turns out that in the cancer bearing state in chronic infection, the immune system is suppressed and you have high levels of substances that are essentially the brakes like CTLA4, PD-1, TIMP-3, LAG-3. CTLA-4 plays a predominant role in the cancer bearing state; you have lots of CTLA4 on your immune cells, which means they don't work very well. What ipilimumab does is that it blocks the braking mechanism. About 15% of the patients will have traditional anti-tumor responses and there will be a clear increment in survival over time. But the survival benefit plateaus out, meaning you have the same proportion of patients alive at 3, 4, 5, 6 years. So some of those patients may well be cured, which is unique.

Dr Salgo then asked the panelists to compare the safety profiles of Provenge and ipilimumab relative to traditional chemotherapies.

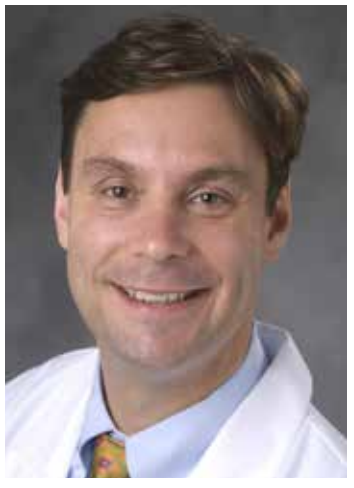
Dr George: With Provenge, because we're activating ex vivo, an infusion reaction occurs following reinfusion, likely due to the induction of cytokines within that cellular mix. It results in a very acute, short-term, generally mild inflammatory profile: fever, chills, and back pain. Less than 3% incidence of grade 3, or what we consider serious adverse events, for any one of these toxicities is observed, which is short-lived, and completely resolves within 24 to 48 hours in the vast majority of cases. So cumulative toxicity, residual toxicity, or end organ damage that are typical of chemotherapy or targeted therapy, in some circumstances, are not observed.

Dr Weber: The beauty of a vaccine against cancer is it will not be toxic. Ipilimumab and PD-1 antibodies are a different scenario because here you're breaking tolerance. If you break the self tolerance of the immune system, it indirectly increases the ability to recognize the cancer, but there will be some collateral damage. About 10% or less of the patients who get ipilimumab will have grade 3 and 4 clinically meaningful serious adverse events that we call IRAEs, or immune-related adverse events, including colitis, inflammation of the pituitary or hypophycitis, low thyroid, rashes, rarely pancreatitis, or hepatitis, all manageable. And I probably spent 8 or 9 years figuring out how to manage these things, and I've written on it extensively. But there will be a cost in side effects.

Dr Salgo then asked the panelists to discuss the associated costs. How can such expensive treatments, sometimes in the range of $90,000 to $100,000, be remunerated?

Dr Weber: Overall survival is the goal. That's what we're judging these drugs by. So, the cost estimate should not be in terms of the cost for that month, but rather in terms of the course of that life.

Dr Kolodziej: However, an unspoken fact is that it doesn't work in everybody. I don't know why it doesn't work in everybody. But as an interested party and not as a payer, I'd love to know who it works in and why.



Daniel J. George, MD

Dr Weber: Well, the FDA would agree because, as you're probably well aware, biomarker development for patient selection is a huge priority at the FDA. It certainly is a huge priority in our field. In fact, my laboratory works on identifying predictive biomarkers for ipilimumab and PD-1 antibodies. With a predictive biomarker, by selecting out patients that won't benefit, the treatment is significantly more effective.

Dr Kolodziej: Patients who do not respond bear that expense, and then the expense of the next therapy down the line, and perhaps have a different clinical course that uses all kinds of other resources. So the real question is who does it work in and why? With precision medicine, you chart patients down a certain course, although those aren't curative therapies.

Dr Weber: But that's why Aetna should be supporting the research into the biomarkers.

Dr Kolodziej: I've been told many times that we're not a research institute, and so I've stopped trying to fight that battle.

Dr Weber: It's not just research. It's a way to make things have a greater value and, essentially, over time, save money.

Dr Salgo then referred back to the question of guidelines. Could the treatment guidelines be changed to incorporate the immunotherapies, and how would it differ from what payers reimburse for and have been reimbursing for?

Dr Weber: The NCCN guidelines now incorporate ipilimumab or a clinical trial for melanoma as your front-line choice or a targeted therapy if BRAF is mutated. So we have a predictive marker now for our BRAF drugs. A genetic change in the tumor is a predictive biomarker, and in its absence the drug is not going to work and might hurt you. So we think the NCCN guidelines, which most of the payers are following, are fair and reasonable. The unspoken issue with immunotherapies is most of them are investigational, and some payers will cover research-related costs and some will not.

Dr Kolodziej: So let's be very clear. It's not Aetna's money that Aetna is spending. Aetna is the administrator for employers who have self-insured plans. They're the payers, while Aetna administers the plan. That's two-thirds of Aetna's business. The other third is people who pay premiums out of their pocket. So you are paying for ineffective therapy today and the responsibility of that is to try to decide whether evidence supports all of us bearing that cost burden or supports the self-insured plans bearing that cost burden. And so we have a fiduciary responsibility to you, if we're your insurer, or it's the responsibility of the self-insured plan. The insurance industry isn't a methodology to answer a research question, but most payers and most national payers agree to pay for research that meets certain criteria.

Dr Salgo: Despite some clinical guidelines which are really very clear, how do you account for some payers that are not paying and are forcing providers not to offer guideline-related therapies?

Dr Kolodziej: I am occasionally asked to review the evidence base for our coverage policy regarding therapies. Aetna has an evidence shop that does just that, and if it's a cancer-specific issue, the person there will come to me for content and I think he tries to be fair.

Dr Weber: But the NCCN guidelines for melanoma say first choice front-line, a clinical trial would be up there with immunotherapy or a targeted therapy for BRAF mutated. Yet, as Dr Kolodziej himself pointed out, the coverage of decisions for going on a phase II or phase III clinical trial can be very inconsistent.

Dr Kolodziej: People who pay the bills can make the decision on what they're going to pay for. So CMS has decided that they'll pay for usual and customary in research and it was a big deal when that finally got approved. All I'm saying is you have that discussion with every single plan....

As a follow-up, Dr Salgo asked the panelists' opinion on the requirement for additional paperwork and hoops to jump through to keep the system functional.

Dr Kolodziej: I personally think it is, yes.

Dr George: Ideally we wouldn't need that but we're recognizing that we're in a dynamic state right now. And what Dr Kolodziej points out is that it's a very heterogeneous state, and I don't think there's going to be a simple solution to get away from paperwork. We're inundated with paperwork in every aspect of our lives, including our professional lives, and payers are just one other aspect of it. But there are ways to streamline it. There are policies, but these are such individual cases. When it comes down to an individual patient in a clinical trial, their eligibility, the appropriateness, the alternative options, etc, there's no way to really have a set policy without being able to have sort of individual review of those cases.

On future directions in cancer immunotherapy:

Dr George: I think this is the most exciting area in cancer research right now. As Dr Weber alluded to, there's a lot of targets we haven't hit yet. We've just started hitting some of these checkpoint inhibitors....Although only in the early years of immunotherapy, what's critical is the credibility that has been established by these therapies in terms of overall survival benefits and long-term disease-free survival benefits with the checkpoint inhibitors. Precision, recognizing for individual patients what those checkpoints might be or what those antigens might be, recognizing newer clinical settings, and how we build on all these findings, is going to be critical.

Currently, we're developing these drugs in the most metastatic refractory settings, but where we envision immunotherapy working best is probably in the more curative settings of adjuvant settings or minimal disease state settings. I hope there's a change in the population of patients we can treat as well as the armamentarium we have to treat them with in a precise and directed way that will make it rational, effective, and hopefully real value. **EBO**

Fine Print of Budget Deal Doesn't Bode Well for SGR Overhaul

Tony Berberabe, MPH, and Mary K. Caffrey

The tiny "raise" touted in the latest temporary fix to Medicare's Sustainable Growth Rate (SGR), which was wrapped inside the bipartisan budget deal President Barack Obama signed December 26, 2013,[1] is anything but good news for oncologists, according to experts from 2 major medical associations.

In fact, according to Ted Okon, executive director of the Community Oncology Alliance (COA), Congress sent signals that chemotherapy administration is going to continue its march into the hospital setting, leaving community oncologists and private practice physicians out in the cold.

News reports on the latest SGR legislation, known as a "patch," touted a purported 0.5% increase in Medicare rates for the first quarter of 2014.[2] But beyond that headline, the real news is less rosy: the SGR stopgap, designed to forestall cuts above 20% to make up for years of shortfalls, includes a provision to keep in place—possibly until 2021—the 2% cuts to Medicare's reimbursement of physicians for patient care and buy-and-bill medication services that were imposed earlier this year due to the sequester.

The Senate approved the overall budget package December 18, 2013, with a 64-36 vote, following a lopsided House vote of 332-94 the week prior.[2]

The votes translate into bad news for community oncologists, according to Okon of COA, a lobbying group for oncologists in community practices. "On January 1, the Centers for Medicare & Medicaid Services will pay less for chemotherapy administration—about 7.4% less," Okon said. "Eventually, CMS will pay 10% less to administer chemotherapy drugs with no cost-base justification."

The latest 3-month fix, following 12 years' worth of stopgap measures to avoid catastrophic cuts to Medicare rates, is designed to let Congress finish designing a plan to permanently eliminate and replace SGR. Critics of SGR call it a flawed instrument that has never kept pace with the true cost of administering care. Congress has vowed to use SGR reform to move Medicare away from a fee-for-service reimbursement model to one that rewards quality care, but many details have yet to be worked out. Left unresolved is how the bill will be funded; that duty will fall to House and Senate appropriators.

Although the military, programs for the needy such as Head Start and Meals on Wheels, and the Transportation Security Administration will benefit from the budget deal, noticeably missing is specific funding for individual federal agencies and programs, including the National Institutes of Health, a critical source of research funding for oncologists, hematologists, and other cancer researchers. It's unlikely that NIH funding will return to pre-sequestration levels, according to a statement from the American Society of Hematologists (ASH).[3]

"The passage of the bill is good news for the nation, with no looming government shutdown, but the demands of the sequester and constraints on NIH funding remain," said Alan Lichtin, MD, chair of government affairs at ASH. Lichtin added that the institution where he works as a hematologist, the Cleveland Clinic, "is not immune to budget constraints [and] has experienced more voluntary retirements. With reimbursement rates going down, Cleveland Clinic has not been able to expand many of its research programs."

The budget deal is disappointing to groups that embraced aspects of an earlier bipartisan plan for SGR reform, drafted by Congress and unveiled on October 30, but now being revised. The day before that announcement, Okon spoke at a Chicago conference, Value-Based Oncology Management, and outlined the "destructive" effects that current Medicare reimbursement policies have had on community clinics.

Since 2005, after Congress altered Medicare cancer drug reimbursement formulas—tying them to average sales price instead of average wholesale price—Okon said 288 clinics have closed, and 469 have been acquired or have a physicians' services agreement with a hospital. "The community share of oncology patients is declining," Okon said.[4]

> *"On January 1, the Centers for Medicare & Medicaid Services will pay less for chemotherapy administration—about 7.4% less. Eventually, CMS will pay 10% less to administer chemotherapy drugs with no cost-base justification."*
>
> **—Ted Okon,**
> Community Oncology Alliance

How the SGR Shortfall Happened

The problem with SGR dates to 1997, when Congress created the formula in an effort to control spending. The formula was supposed to set realistic yearly and cumulative spending targets; if the cost of care exceeded the target in any given year, rates would be cut the following year to make up the difference.

Ted Okon

However, inaccurate forecasts meant actual Medicare Part B spending has exceeded the target for more than a decade. American Medical Association (AMA) President Ardis Hoven, MD, told *MedPage Today* after the October 30 announcement that, each year, the "sword of Damocles" would hang over physicians' heads as they waited for Congress to pass legislation to thwart the automatic cuts.[5] Yet the longer Congress failed to fix SGR, the worse the problem grew.

How big is the problem? Estimates for getting rid of SGR include $377 billion for 2012 and $139 billion for 2013, and there are no good answers on how to address the problem. When asked how the repeal would be funded, AMA's Hoven said, "I don't think we really know."[5] Some accounts attribute the shrinking SGR shortfall to the fact that physicians have already sustained so many cuts.

Problems with Medicare's dysfunctional reimbursement model have hit oncology especially hard, and the effects of the federal sequester have only made things worse, Okon explained in Chicago. Oncology's buy-and-bill system of administering increasingly expensive medications, the diversity of disease states, and the fact that so many cancer patients are older and reliant on Medicare mean an outdated reimbursement model is acutely felt in oncology. According to the American Cancer Society's 2013 report, 77% of all new cancers are diagnosed in persons 55 years or older.[6]

The lack of resolution has not been good for doctors or patients, Okon told the Chicago gathering. More and more patients who need chemotherapy have been pushed into hospitals, where costs are higher. Shortages of key chemotherapy drugs, especially generics, have emerged, along with parts of the country where care is limited. **EBO**

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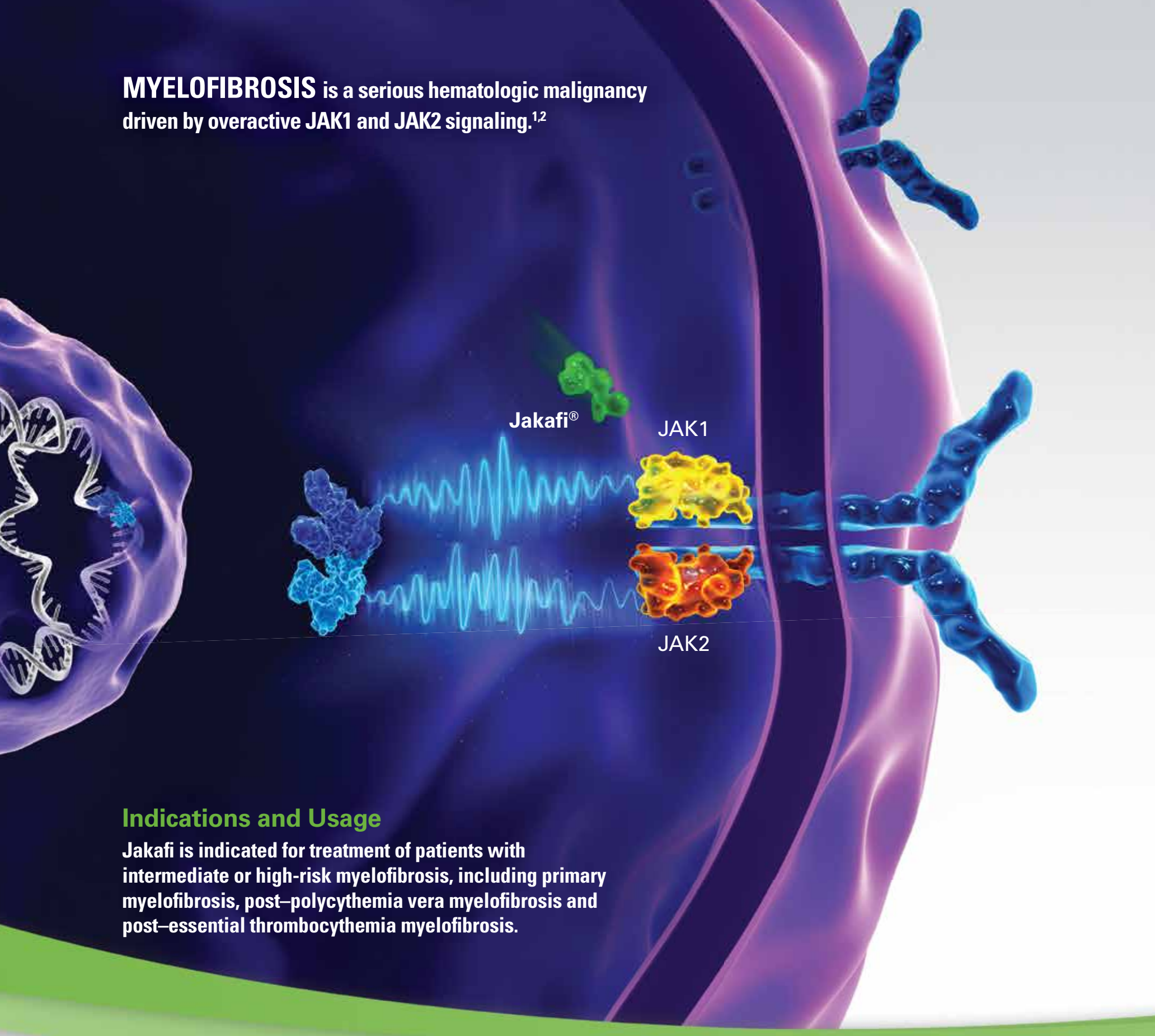
MYELOFIBROSIS is a serious hematologic malignancy driven by overactive JAK1 and JAK2 signaling.[1,2]



Indications and Usage

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

Important Safety Information

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects, with the most frequent being thrombocytopenia and anemia. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Thrombocytopenia was generally reversible and was usually managed by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC $<0.5 \times 10^9$/L) was generally reversible. Withhold Jakafi until recovery
- The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache
- Serious bacterial, mycobacterial, fungal and viral infections may occur. Active serious infections should have resolved before starting Jakafi. Observe patients receiving Jakafi for signs and symptoms of infection and initiate appropriate treatment promptly. Advise patients about early signs and symptoms of herpes zoster and to seek early treatment

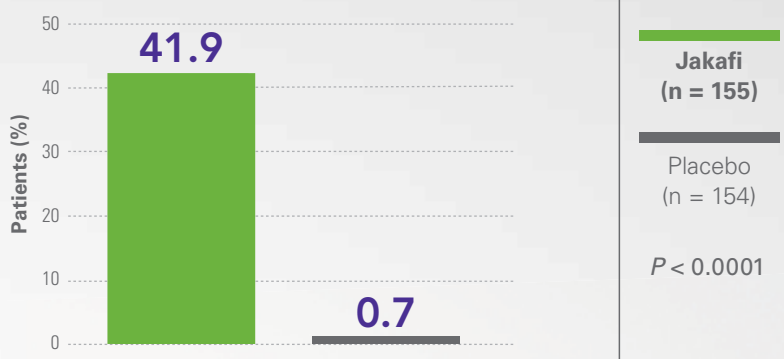
Incyte

The first and only FDA-approved drug treatment for intermediate or high-risk **MYELOFIBROSIS**[3,4]

Target the JAK pathway—treat the disease

Jakafi inhibits both JAK1 and JAK2 signaling, an underlying mechanism of disease, and significantly improves splenomegaly and symptoms[4,5]

COMFORT-I: Percentage of patients with ≥35% reduction in spleen volume from baseline to Week 24[4,5,a]



COMFORT-I: Percentage of patients with ≥50% improvement in TSS at Week 24[4,5,a,b]

COMFORT-I = COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment (I); TSS = Total Symptom Score.

- Efficacy was seen with Jakafi in both *JAK2*V617F-positive and *JAK2*V617F-negative patients, relative to placebo[6,7]

Consider Jakafi upon diagnosis for your patients with intermediate-1, intermediate-2 or high-risk myelofibrosis

JAK = Janus kinase.

- Progressive multifocal leukoencephalopathy (PML) has been reported with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate
- A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breast-feed

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

[a]As studied in COMFORT-I, a randomized, double-blind, placebo-controlled phase III study with 309 total patients. The primary endpoint was the proportion of subjects achieving a ≥35% reduction in spleen volume from baseline to Week 24. A secondary endpoint was the proportion of subjects with a ≥50% reduction in TSS from baseline to Week 24.[4,5]

[b]TSS was captured by a daily patient diary (MFSAF v2.0). TSS encompasses debilitating symptoms of myelofibrosis: abdominal discomfort, early satiety, pain under left ribs, pruritus, night sweats and bone/muscle pain. Symptom scores ranged from 0 to 10 with 0 representing symptoms "absent" and 10 representing "worst imaginable" symptoms. These scores were added to create the daily total score, which has a maximum of 60. At baseline, mean TSS was 18.0 in the Jakafi group and 16.5 in the placebo group.[4,5]

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Jakafi®
ruxolitinib (tablets)

Jakafi®
ruxolitinib (tablets)

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

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

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [*see Dosage and Administration (2.1) in Full Prescribing Information*]. Thrombocytopenia was generally reversible and was usually managed by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [*see Dosage and Administration (2.2) in Full Prescribing Information, and Adverse Reactions*]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 X 10^9/L) was generally reversible. Withhold Jakafi until recovery [*see Adverse Reactions*]. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [*see Dosage and Administration (2.2) in Full Prescribing Information, and Adverse Reactions*]. **Risk of Infection** Serious bacterial, mycobacterial, fungal and viral infections may occur. Active serious infections should have resolved before starting therapy with Jakafi. Observe patients receiving Jakafi for signs and symptoms of infection and initiate appropriate treatment promptly. *PML* Progressive multifocal leukoencephalopathy (PML) has been reported with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate. *Herpes Zoster* Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [*see Adverse Reactions*].

ADVERSE REACTIONS The following serious adverse reactions are discussed in greater detail in other sections of the labeling: • Myelosuppression [*see Warnings and Precautions*]; • Risk of Infection [*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 safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with myelofibrosis in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 88.7% of patients treated for more than 6 months and 24.6% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In a double-blind, randomized, placebo-controlled study of Jakafi, 155 patients were treated with Jakafi. The most frequent adverse drug reactions were thrombocytopenia and anemia [*see Table 2*]. Thrombocytopenia, anemia and neutropenia are dose related effects. The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache [*see Table 1*]. Discontinuation for adverse events, regardless of causality, was observed in 11.0% of patients treated with Jakafi and 10.6% of patients treated with placebo. Following interruption or discontinuation of Jakafi, symptoms of myelofibrosis generally return to pretreatment levels over a period of approximately 1 week. There have been isolated cases of patients discontinuing Jakafi during acute intercurrent illnesses after which the patient's clinical course continued to worsen; however, it has not been established whether discontinuation of therapy contributed to the clinical course in these patients. When discontinuing therapy for reasons other than thrombocytopenia, gradual tapering of the dose of Jakafi may be considered [*see Dosage and Administration (2.9) in Full Prescribing Information*]. Table 1 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

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

	Jakafi (N=155)			Placebo (N=151)		
Adverse Reactions	**All Grades[a] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Bruising[b]	23.2	0.6	0	14.6	0	0
Dizziness[c]	18.1	0.6	0	7.3	0	0
Headache	14.8	0	0	5.3	0	0
Urinary Tract Infections[d]	9.0	0	0	5.3	0.7	0.7
Weight Gain[e]	7.1	0.6	0	1.3	0.7	0
Flatulence	5.2	0	0	0.7	0	0
Herpes Zoster[f]	1.9	0	0	0.7	0	0

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

Description of Selected Adverse Drug Reactions Anemia In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (0.3%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients. **Thrombocytopenia** In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50 X 10^9/L was 14 days. Platelet transfusions were administered to 4.7% of patients receiving Jakafi and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving Jakafi and 0.9% of patients receiving control regimens. Patients with a platelet count of 100 X 10^9/L to 200 X 10^9/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 X 10^9/L (16.5% versus 7.2%). **Neutropenia** In the two Phase 3 clinical studies, 1.0% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

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

	Jakafi (N=155)			Placebo (N=151)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Thrombocytopenia	69.7	9.0	3.9	30.5	1.3	0
Anemia	96.1	34.2	11.0	86.8	15.9	3.3
Neutropenia	18.7	5.2	1.9	4.0	0.7	1.3

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

Additional Data from the Placebo-controlled Study 25.2% of patients treated with Jakafi and 7.3% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 1.9% for Jakafi with 1.3% Grade 3 and no Grade 4 ALT elevations. 17.4% of patients treated with Jakafi and 6.0% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was 0.6% for Jakafi with no Grade 3 or 4 AST elevations. 16.8% of patients treated with Jakafi and 0.7% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was 0.6% for Jakafi with no Grade 3 or 4 cholesterol elevations.

DRUG INTERACTIONS Drugs That Inhibit or Induce Cytochrome P450 Enzymes Ruxolitinib is predominantly metabolized by CYP3A4. **Strong CYP3A4 inhibitors:** The C_{max} and AUC of ruxolitinib increased 33% and 91%, respectively, with Jakafi administration (10 mg single dose) following ketoconazole 200 mg twice daily for four days, compared to receiving Jakafi alone in healthy subjects. The half-life was also prolonged from 3.7 to 6.0 hours with concurrent use of ketoconazole. The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding ruxolitinib AUC following concurrent administration with ketoconazole. When administering Jakafi with strong CYP3A4 inhibitors a dose reduction is recommended [*see Dosage and Administration (2.7) in Full Prescribing Information*]. Patients should be closely monitored and the dose titrated based on safety and efficacy. **Mild or moderate CYP3A4 inhibitors:** There was an 8% and 27% increase in the C_{max} and AUC of ruxolitinib, respectively, with Jakafi administration (10 mg single dose) following erythromycin, a moderate CYP3A4 inhibitor, at 500 mg twice daily for 4 days, compared to receiving Jakafi alone in healthy subjects. The change in the pharmacodynamic marker, pSTAT3 inhibition was consistent with the corresponding exposure information. No dose adjustment is recommended when Jakafi is coadministered with mild or moderate CYP3A4 inhibitors (eg, erythromycin). **CYP3A4 inducers:** The C_{max} and AUC of ruxolitinib decreased 32% and 61%, respectively, with Jakafi administration (50 mg single dose) following rifampin 600 mg once daily for 10 days, compared to receiving Jakafi alone in healthy subjects. In addition, the relative exposure to ruxolitinib's active metabolites increased approximately 100%. This increase may partially explain the reported disproportionate 10% reduction in the pharmacodynamic marker pSTAT3 inhibition. No dose adjustment is recommended when Jakafi is coadministered with a CYP3A4 inducer. Patients should be closely monitored and the dose titrated based on safety and efficacy.

USE IN SPECIFIC POPULATIONS Pregnancy Pregnancy Category C: There are no adequate and well-controlled studies of Jakafi in pregnant women. In embryofetal toxicity studies, treatment with ruxolitinib resulted in an increase in late resorptions and reduced fetal weights at maternally toxic doses. Jakafi should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There was no evidence of teratogenicity. However, decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). **Nursing Mothers** It is not known whether ruxolitinib is excreted in human milk. Ruxolitinib and/or its metabolites were excreted in the milk of lactating rats with a concentration that was 13-fold the maternal plasma. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Jakafi, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** The safety and effectiveness of Jakafi in pediatric patients have not been established. **Geriatric Use** Of the total number of myelofibrosis patients in clinical studies with Jakafi, 51.9% were 65 years of age and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. **Renal Impairment** The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects [CrCl 72-164 mL/min (N=8)] and in subjects with mild [CrCl 53-83 mL/min (N=8)], moderate [CrCl 38-57 mL/min (N=8)], or severe renal impairment [CrCl 15-51 mL/min (N=8)]. Eight (8) additional subjects with end stage renal disease requiring hemodialysis were also enrolled. The pharmacokinetics of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function. However, plasma AUC values of ruxolitinib metabolites increased with increasing severity of renal impairment. This was most marked in the subjects with end stage renal disease requiring hemodialysis. The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in metabolite exposure. Ruxolitinib is not removed by dialysis; however, the removal of some active metabolites by dialysis cannot be ruled out. When administering Jakafi to patients with moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min) with a platelet count between 100 X 10^9/L and 150 X 10^9/L and patients with end stage renal disease on dialysis a dose reduction is recommended [*see Dosage and Administration (2.8) in Full Prescribing Information*]. **Hepatic Impairment** The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects (N=8) and in subjects with mild [Child-Pugh A (N=8)], moderate [Child-Pugh B (N=8)], or severe hepatic impairment [Child-Pugh C (N=8)]. The mean AUC for ruxolitinib was increased by 87%, 28% and 65%, respectively, in patients with mild, moderate and severe hepatic impairment compared to patients with normal hepatic function. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1-5.0 hours versus 2.8 hours). The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in ruxolitinib exposure except in the severe (Child-Pugh C) hepatic impairment cohort where the pharmacodynamic activity was more prolonged in some subjects than expected based on plasma concentrations of ruxolitinib. When administering Jakafi to patients with any degree of hepatic impairment and with a platelet count between 100 X 10^9/L and 150 X 10^9/L, a dose reduction is recommended [*see Dosage and Administration (2.8) in Full Prescribing Information*].

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Adjuvant Pre- or Post Operative Chemotherapy Does Not Improve Survival in Rectal Cancer

Surabhi Dangi-Garimella, PhD

Researchers found improved local control but not improved overall survival in a long-term study that examined the addition of chemotherapy to pre-operative radiotherapy for patients with rectal cancer. The results from the European Organisation for the Research and Treatment of Cancer (EORTC) trial 22921 were published in the February 2014 issue of *The Lancet Oncology*.[1]

The study randomly assigned 1011 patients with clinical stage T3 or T4 resectable rectal cancer to receive pre-operative radiotherapy, with or without concomitant chemotherapy, before surgery followed by either adjuvant chemotherapy or surveillance. Radiotherapy consisted of 45 Gy to the posterior pelvis in 25 fractions of 1·8 Gy over 5 weeks. Each course of chemotherapy consisted of fluorouracil (350 mg/m^2 per day intravenous bolus) and folinic acid (leucovorin; 20 mg/m^2 per day intravenous bolus). Two courses were administered (during weeks 1 and 5 of radiotherapy) for pre-operative chemotherapy, while adjuvant chemotherapy was given in 4 cycles, every 3 weeks. The primary end point was overall survival (OS).

Following a median follow-up of 10.4 years, 10-year OS was 49.4% for the pre-operative radiotherapy group, 50.7% for the pre-operative radiotherapy and chemotherapy group, 51.8% for the adjuvant chemotherapy group, and 48.4% for the surveillance group. The 10-year disease-free survival was also quite similar between the groups: 44.2%, 46.4%, 47.0%, and 43.7%, respectively. However, incidence of local relapse at 10 years was highest with radiotherapy alone (22.4%), followed by radiotherapy and adjuvant chemotherapy (14.5%), neoadjuvant radiotherapy and chemotherapy (11.8%), and adjuvant and neoadjuvant chemotherapy (11.7%). The frequency of long-term side effects did not differ between the groups.

The authors concluded that adjuvant fluorouracil-based chemotherapy after preoperative radiotherapy (with or without chemotherapy) does not affect disease-free survival or OS and that new treatment strategies incorporating neoadjuvant chemotherapy are required.

Research in this field continues to explore the optimal duration of chemotherapy for patients with colorectal cancer (CRC), with the standard duration declining from 18 months to the current standard of 12 cycles over 6 months, and a 3-month course is also being examined. According to Claus-Henning Kohne, MD, PhD, chairman of the Department of Hematology and Oncology, Klinikum Oldenburg, Germany, "The most exciting research currently in stage III CRC is the examination of ever-shorter duration of treatment."[2] **EBO**

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Promising Results Halt Phase III Studies of Idelalisib

Silas Inman

A phase III study of the PI3K-delta inhibitor idelalisib in combination with rituximab (Rituxan) has been stopped early following a positive interim analysis, according to a statement from Gilead Sciences, Inc, the company developing the drug.

The randomized trial, labeled Study 116, investigated the combination as a treatment for chemotherapy-ineligible patients with previously treated chronic lymphocytic leukemia (CLL). The decision to stop the trial early followed a recommendation from an independent data monitoring committee that found a highly statistically significant prolongation in the primary end point of progression-free survival (PFS). Subsequently, patients on the control arm receiving rituximab plus placebo are now eligible for treatment with idelalisib in an extension study.

Susan M. O'Brien, MD

Idelalisib, a first-in-class selective PI3K-delta inhibitor, is thought to be effective in B-cell malignancies due to the role of PI3K-delta in the activation, proliferation, and survival of B cells, a rationale that was confirmed in early-stage trials.

"This is the first phase III study to report positive results for a new class of targeted therapies that inhibit B-cell receptor signaling as a major component of their mechanism of action, an important area of focus in the development of chemotherapy-free regimens in CLL and other B-cell malignancies," said Norbert W. Bischofberger, PhD, executive vice president of research and development and chief scientific officer at Gilead, in the statement.

The study enrolled a total of 220 patients, all of whom had previously treated recurrent CLL with measurable lymphadenopathy. Patients in the trial were randomized in a 1:1 ratio to receive idelalisib at a 150 mg dose twice a day in combination with intravenous rituximab at an initial dose of 375-mg/m^2 followed by 500 mg/m^2 or rituximab and placebo. Patients who progressed were eligible to receive idelalisib therapy in a double-blind extension study.

The phase III study was launched on the basis of results from a phase I trial examining the combination of idelalisib with rituximab and/or bendamustine for patients with previously treated CLL, presented at the 2012 meeting of the American Society of Hematology. In that study, 19 patients who had received a median of 2 prior therapies took idelalisib at 150 mg twice a day in combination with weekly rituximab at 375 mg/m^2. In the intent-to-treat population, the overall response rate (ORR) was 78%, the 1-year PFS rate was 74%, and 84% of patients experienced a lymph node response (shrinkage ≥50%) resulting in marked reductions in lymphadenopathy.

The combination of idelalisib, rituximab, and bendamustine (Treanda) presented the best response, with an ORR of 87%, a 1-year PFS rate of 87%, and lymph node response in 87% of the 15 patients. A randomized phase III study examining the combination of idelalisib, rituximab, and bendamustine is recruiting patients with previously treated CLL (NCT01569295).

The early stop of the phase III trial indicates a promising treatment with the potential for regulatory approval, although early discontinuation of randomized clinical trials based on evidence of benefit is controversial, with research suggesting an overestimation of treatment effects.

In its announcement, Gilead stated that it had informed the US Food and Drug Administration (FDA) of its decision to stop the trial. The company is

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engaged in conversations regarding a potential regulatory filing for idelalisib in CLL. In September 2013, Gilead submitted a New Drug Application to the FDA for approval of idelalisib for the treatment of patients with indolent non-Hodgkin's lymphoma (iNHL).

That submission was based on data from a single-arm, open-label phase II study of 125 patients with iNHL who were refractory to rituximab and an alkylating-agent-containing chemotherapy. In an interim analysis of this study, single-agent idelalisib achieved an ORR of 53.6%, with a median duration of response of 11.9 months, median PFS of 11.4 months, and lymph node shrinkage experienced in 89% of patients.

Additionally, according to results from a phase II trial presented at the 2013 annual meeting of the American Society of Clinical Oncology, idelalisib plus rituximab has demonstrated promising results in treatment-naïve patients with CLL. In that study, patients who were ≥65 years old with previously untreated CLL or small lymphocytic lymphoma received idelalisib at 150 mg twice a day combined with weekly rituximab at 375 mg/m^2. At a 24-month analysis, the combination was found to be highly active in treatment-naïve elderly patients. The trial found a Kaplan-Meier estimated PFS benefit of 93%. Moreover, the combination achieved a complete response rate of 19% and an ORR of 97%.

At the time of the presentation, the principal investigator on the study, Susan M. O'Brien, MD, Ashbel Smith Professor of Medicine in the Department of Leukemia at the University of Texas MD Anderson Cancer Center, said, "The high overall response rate and durable disease control observed in this phase II study suggest that idelalisib in combination with rituximab could become an important therapeutic option for CLL patients new to treatment." **EBO**

GSK Drug Combination Approved for Advanced Melanoma

Silas Inman

The US Food and Drug Administration (FDA) has granted an accelerated approval to the combination of the MEK inhibitor trametinib (Mekinist) and the BRAF inhibitor dabrafenib (Tafinlar), both developed by GlaxoSmithKline (GSK), as a treatment for patients with unresectable or metastatic melanoma who harbor a *BRAF V600E* or *V600K* mutation. The approval was based on results from an open-label phase I/II trial, which showed that trametinib combined with dabrafenib nearly doubled the duration of response and significantly improved overall response rates (ORR) compared with dabrafenib alone.

Richard Pazdur, MD

Both drugs were approved as single agents in May 2013 along with a companion diagnostic. This is the first approval for a targeted therapy combination in advanced melanoma.

"Mekinist and Tafinlar are the first drugs approved for the combination treatment of melanoma," said Richard Pazdur, MD, director of the Office of Hematology and Oncology Products at the FDA's Center for Drug Evaluation and Research. "Their development for combination use is based on the strong understanding of the biological pathways of the disease. This approval illustrates the value of continuing to study drugs in combination for clinical development."

The study was based on the rationale that a more complete inhibition of the mitogen-activated protein kinase pathway could help overcome the resistance developed by 50% of the patients within 6 to 7 months following the administration of a single-agent BRAF or MEK inhibitor. The phase I/II study was conducted in 4 segments, with phase II generating the majority of information regarding clinical activity. In this segment of the trial, 162 patients with advanced melanoma and *BRAF V600E/K* mutations were randomized in a 1:1:1 ratio, with 54 patients in each arm who had not previously received BRAF or MEK inhibitors. Patient characteristics were balanced between arms, with an ECOG (Eastern Cooperative Oncology Group) performance status of 0 or 1.

The patients received 150 mg of dabrafenib twice a day, plus 1 mg of trametinib once daily (combination 150/1), or 150 mg of dabrafenib twice a day plus 2 mg trametinib once daily (combination 150/2). Patients in the control group received single-agent dabrafenib at 150 mg twice a day. The primary endpoints included progression-free survival (PFS), ORR, and duration of response. Overall survival (OS) was assessed as a secondary end point; however, crossover was allowed following progression.

The trial results confirmed the superiority of the 150/2 combination, which was chosen as the FDA-approved dose. Compared with the control (54%) the ORR of the 150/2 group was observed at 76% ($P = 0.03$), and the median duration of response was 5.6 months compared with 10.5 months, respectively. The median PFS with the 150/2 combination was 9.4 months compared with 5.8 months for the control (hazard ratio [HR] = 0.39; 95% confidence interval [CI], 0.25-0.62; $P < .001$). However, the HR for PFS by independent review was less pronounced at 0.55 (95% CI, 0.33-0.93; $P = 0.02$).

Paolo Paoletti, GSK

After 1 year, 41% of patients in the 150/2 group were alive and progression-free compared with only 9% in the control group ($P < .001$), and approximately 80% of patients crossed over from the control group to the 150/2 group following disease progression.

The BRAF and MEK inhibitor combination significantly reduced the incidence of secondary cutaneous squamous cell carcinoma, which occurred in 19% of patients receiving dabrafenib monotherapy compared with 2% for combination 150/1 ($P = .004$) and 7% for combination 150/2 ($P = .09$). The most frequent all-grade side effects associated with the combination were pyrexia (71%) and chills (58%), with severe pyrexia observed in 19% of patients in the 150/1 group, 25% in the 150/2 group, and in 2% in the control group.

Paolo Paoletti, MD, president of oncology at GSK, said in a press release, "This approval marks another key moment in what continues to be a rapid evolution of the treatment landscape for metastatic melanoma patients. Combining agents that target different mechanisms regulating the growth of cancer cells is one of the promising areas in cancer research. We are proud that the first approved combination of targeted therapies in metastatic melanoma is Mekinist and Tafinlar, and our hope is that it will become part of the new standard of care for appropriate patients with *BRAF V600E* or *V600K* mutation-positive metastatic melanoma."

To support the accelerated approval, the combination of dabrafenib and trametinib is being explored in a number of phase III trials for patients with metastatic melanoma. In the phase III placebo-controlled COMBI-AD study, dabrafenib in combination with trametinib is being explored as an adjuvant treatment for patients with high-risk melanoma with a *BRAF V600* mutation following surgical resection. **EBO**

Reversing Halt, FDA Reauthorizes Sale of Ponatinib

Andrew J. Roth

The US Food and Drug Administration (FDA) has approved revised US Prescribing Information (USPI) and a Risk Evaluation and Mitigation Strategy (REMS) for ponatinib, marketed as Iclusig, according to an announcement from Ariad Pharmaceuticals, Inc, the company developing the drug. The USPI and REMS allow for the immediate resumption of ponatinib's marketing and commercial distribution. The USPI also includes a revised indication statement and a boxed warning, with alerts to the risk of vascular occlusive events and heart failure. The USPI also includes dosing recommendations, which remain at 45 mg daily.

The approval of the revised USPI for ponatinib was based on a review of clinical trial data, including a 24-month follow-up of the pivotal PACE (Ponatinib Ph ALL and CML Evaluation) trial, which served as the basis for the drug's approval in 2012.

Approximately 640 patients had obtained ponatinib through commercial channels in the United States at the end of October 2013. Ponatinib has since been made available on a case-by-case basis to 350 patients through emergency and single-patient investigational new drug (IND) applications.

"In less than 2 months of suspending marketing and commercial distribution of Iclusig in the US, we addressed the issues raised by the FDA and now are able to market and distribute Iclusig again in the US," Harvey J. Berger, MD, chairman and chief executive officer of Ariad, said in a statement. "As we look ahead to relaunching Iclusig in the US and fulfilling our post-marketing requirements, we will continue to focus on understanding the benefits and risks of Iclusig treatment in patients with resistant or intolerant Philadelphia-positive leukemias."

Ponatinib is approved for adult patients with:

- Chronic phase, accelerated phase, or blast phase T315I-positive chronic myeloid leukemia (CML)
- T315I-positive Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL)
- Chronic phase, accelerated phase, or blast phase CML or Ph+ ALL for whom no other tyrosine-kinase inhibitor therapy is indicated

Harvey J. Berger, MD

The clinical development of ponatinib was placed on hold in early October 2013 while the FDA investigated the adverse events associated with the drug. This was shortly followed by the early termination of the phase III EPIC (Evaluation of Ponatinib versus Imatinib in CML) trial, which was examining ponatinib in the frontline setting for untreated patients with CML. The suspension in distribution followed discussions between Ariad and the FDA.

Marty Duvall, executive vice president and chief commercial officer of Ariad, said that commercial and medical affairs teams will be deployed by mid-January. Duvall said distribution of ponatinib will then begin and the company expects the drug will be "cash-flow positive from the onset." Until then, the drug will be distributed with the IND mechanism. **EBO**

Post Marketing Research No Longer an Afterthought With Targeted Therapies

Mary K. Caffrey

With the rise of targeted therapies, the days of letting doctors report informally on unexpected reactions to new cancer drugs are long gone. The change signals a larger role for phase IV, the post marketing research step in the approval process.

Accelerated approvals can take months, if not years, off the time it takes to get a life-saving drug to a cancer patient, but they may occur without sufficient efficacy data. So, today those approvals typically come with a catch: pharmaceutical companies must closely monitor patients and report reactions to toxicity. The US Food and Drug Administration (FDA) has created the Risk Evaluation and Mitigation Strategies (REMS) program, for drugs approved where the risk-to-benefit ratio "may not be apparent in all clinically relevant scenarios,"[1] according to Mark Crowther, MD, of St. Joseph's Hospital in Hamilton, Ontario.

Crowther was part of the education session, "A Fresh Look at Drug Approval: Moving Away from Tradition," offered at the 55th American Society of Hematology Annual Meeting and Exposition in New Orleans, December 7-10, 2013.

The "post licensure" monitoring programs represent the balancing act the FDA faces in trying to hasten the time it takes to get new therapies into the market. Long approval periods not only keep beneficial drugs away from patients, they also drive up costs. Thus, the FDA awards "breakthrough" designations when it can be shown that a drug "may (provide) substantial improvement on at least one clinically significant end point over available therapy."[1]

Mark Crowther, MD

Such research is obviously beneficial to patients. Sometimes the size of a clinical trial, or its design, prevents researchers from detecting reactions that become apparent once a drug reaches the general population. Crowther cited the case of cervistatin, a cholesterol-lowering agent, which was taken off the market after reports of deaths from rhabdomyolysis, especially among patients also taking gembfibrozil.

But data collection benefits drug developers, too. Not only does the combination of accelerated approval and post marketing research get drugs to market quickly for their original purpose, but phase IV research "may lead to new indications," Crowther said.

Compared with phase IV research of earlier eras, today's studies are robust and systematic. Self-reports, which Crowther dismissed as useless, have been replaced with large data sets and obligatory, uniform reporting. The "real time" aspect of these methods allows regulators to closely monitor new therapies and act quickly if there's a problem.

Another game changer has been the FDA's Sentinel project, launched in 2008. This national system, which will become more powerful as electronic record keeping takes hold, lets the FDA track not only toxicity reactions, but also drug and dosing changes made in response to its warnings. What's more, unlike post market research done by pharmaceutical companies, this project offers the independence of a third party.

(For a recent example, see the related story above on the FDA's work with Ariad Pharmaceuticals on ponatinib.) **EBO**

Reference

1. Crowther M. Phase 4 research: what happens when the rubber meets the road? *Hematology Am Soc Hematol Edu Program.* 2013;2013:15-18.

THE AMERICAN JOURNAL OF MANAGED CARE

When Less Is More: Results Herald "Paradigm Shift" in Treating Newly Diagnosed Multiple Myeloma Patients

Mary K. Caffrey

Treating newly diagnosed patients—even older ones—with a combination of lenalidomide, marketed by Celgene as Revlimid, and low-dose dexamethasone, a steroid, seems likely to become the new treatment standard for multiple myeloma, based on the presentation of a massive, multinational phase III study[1] presented in December at the 55th American Society of Hematology (ASH) Meeting and Exhibition in New Orleans. Lenalidomide is a vascular endothelial growth factor inhibitor.

Thierry Facon, MD, lead author on the abstract, outlined results from the FIRST (Frontline Investigation Of Lenalidomide + Dexamethasone Versus Standard Thalidomide) Trial, which asked whether the standard of treating newly diagnosed older patients with melphalan and thalidomide first still makes sense. Facon, of the Lille Regional University in Lille, France, and his colleagues found it does not, based on results from 1623 patients from 243 cancer centers in 18 countries. In the study, sponsored by Celgene and the Intergroupe Francophone du Myelome (IFM), all patients were at least 65 years of age and the median age was 73 years; this is key because the drug combination that FIRST examined has been used in younger patients, but not among older patients who make up most of the multiple myeloma population.

Patients were randomly assigned to 3 treatment groups: the first received treatment with the lenalidomide-dexamethasone combination—called Lex-Dex—for 18 months, the second received treatment with melphalan, prednisone, and thalidomide (MPT) for 18 months, and the third received the Lex-Dex combo continuously, or until the disease progressed. Under current standards of care, therapy ends after several months because patients begin to experience side effects.

At 37 months, progression-free survival (PFS) among those taking the Lex-Dex combination continuously was 25.5 months. For the other 2 groups, PFS was almost the same, with the Lex-Dex group seeing 20.7 months on average and the MPT group seeing 21.2 months, which represented a 28% reduction in risk progression for the group taking Lex-Dex continuously.

In the session, Facon said that long-term results for overall survival (OS) are not yet mature, but at the 4-year mark, OS was 59.4% for the continuous Lex-Dex group, 55.7% for the group that received Lex-Dex for 18 months, and 51.4% for the MPT group.

What's more, Facon said, is that cytogenetic profiles show that 762 patients were high risk; some were already suffering loss of renal function. Unlike populations typically included in clinical trials, Facon said, "This population is somewhat close to a real-life population."

A capacity crowd filled the giant hall at the plenary session to hear Dr Facon's presentation, after which a questioner commented, "This is a shift in the paradigm." Adverse effects (AEs) were dramatically reduced for the Lex-Dex groups compared with MPT, and remained "manageable" even for those on continuous therapy, Facon said. Grade 3 and 4 AEs for the continuous Lex-Dex arm versus the MPT arm included: neutropenia, 28% versus 45%; thrombocytopenia, 8% versus 11%; infection, 29% versus 17%; neuropathy, 5% versus 15%; and deep-vein thrombosis, 5% versus 3%.

Despite the better results for continuous therapy in the trial, it is too soon to say whether it will become a standard with Lex-Dex therapy. Although less toxic than MPT, continuous therapy does present issues of side effects. But the bigger challenge may be cost: Revlimid prices range between $12,700 and $13,300 a month, based on online pharmacy prices from GoodRx. **EBO**

Reference

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Collaboration Between Academia and Pharma to Bring New Therapies to Market More Important Than Ever

Mary K. Caffrey

With grants from government sources looking less certain, partnerships between academic research centers and pharmaceutical companies are more important than ever to keep breakthrough hematology therapies in the pipeline, said Burt Adelman, MD, a hematologist who serves as executive vice president and chief medical officer for Dyax Inc.

Adelman, long affiliated with Brigham and Women's Hospital in Boston, Massachusetts, told a gathering at the 55th American Society of Hematology (ASH) Annual Meeting and Exposition in New Orleans, held December 7-10, 2013, that traditional drug development models inside pharmaceutical companies lack the one thing that academic medical centers have in abundance: access to patients in real-world settings.

It is important, he said, for the best and brightest in academia to promote themselves to industry, and to not assume that pharmaceutical companies will find them. Try as they might to follow the literature, Adelman said, "We don't know everyone, no matter how much exciting work you may have going on."

Burt Adleman, MD

And the pharmaceutical industry has hit a plateau of sorts, he said. In 2012, worldwide drug sales fell 1.6%; while 43 new drugs were approved by the US Food and Drug Administration (FDA) in 2012, the 13-year average has been 32. What is more alarming is that between 2013 and 2019, $230 billion of US drug sales are at risk due to patent expiration. "Pharma is facing the innovation stagnation dilemma," he said.[1]

This means opportunities for partnerships with academic centers, who tend to bring more of the "breakthroughs" to the FDA, compared with industry, which tends to bring more of the "me too," drugs.

At the same time, Adelman said, it is in academia's interest to reach out to industry. The National Institutes of Health cut $1.55 billion from its FY 2013 budget; with the effects of the federal sequester continuing and no "grand bargain" in sight, things do not look promising for US government support for research.

In fact, the bipartisan budget agreement reached less than 2 weeks after the meeting drew this response from ASH:

"The passage of the bill is good news for the nation, with no looming government shutdown, but the demands of the sequester and constraints on NIH funding remain," said Alan Lichtin, MD, chair of government affairs at ASH. Lichtin added that the institution where he works as a hematologist, the Cleveland Clinic, "is not immune to budget constraints [and] has experienced more voluntary retirements. With reimbursement rates going down, Cleveland Clinic

has not been able to expand many of its research programs."[2]

Who creates drugs? Adelman cited data from 1998 to 2007, which broke out new drugs from the following:

- Pharmaceutical companies, 147.2 new drugs, or 58%
- Biotech, 44.1 drugs, or 18%
- University transfer, 60.7 drugs; 24%

Adelman said he understands the reluctance of academic researchers to share ideas with industry; there is a fear that good work will be stolen, and the scholar will not reap the rewards. However, he said, as it stands, research institutions are not benefiting from the spending on healthcare, which in 2011 hit $2.7 trillion, including 10% on prescription drugs.

"Very little of that annual $268 billion goes back to investigators of academic institutions. It's a big number to not be participating in," he said.

And pharmaceutical companies maintain an enormous research effort: the total capital cost of the average new drug that comes to market is between $800 million and $1 billion; of course, that includes the cost of the many attempts that fail. "There's a less than 10% success rate across all therapeutic areas; the average development time is 10 years," Adelman said. As he explained, researchers inside pharmaceutical companies are more risk-averse than those in academia with those kinds of statistics. Lack of efficacy, he said, is the main reason for drug failure, and often this is not discovered until the end of phase II or even phase III.

He cited statistics that said industry would continue to put $138 billion into research and development in 2014. Without enough new drugs coming to market, and more being spent on research, he said, "a cynic" would conclude that increased profits can only come from increased drug prices, both new and existing. Yet, there is pressure for that not to continue.

In the meantime, in hematology especially, the race is on to find better therapies to reduce the toxicity of older chemotherapies. "You cannot practice modern hematology without a prescription pad," Adelman said. "We are constantly in need of new solutions to difficult problems."

There are models in place for researchers to work either within their academic institution or directly with pharmaceutical companies to transfer technology. "The challenge is to figure out how to do this in a more reproducible way," Adelman said. "If 24% of 252 drugs trace to academia, it is unlikely that 24% of the revenue is going to the institution."

What does industry need?

"We need access to valued targets and technology. We need translational models; research tools. We need your patients, and we need your insights," Dr Adelman said. There are also mundane needs, like access to diagnostic tools, such as MRIs, CT scans, and pathology labs.

Academics interested in sharing should work through their institutions to understand the rules, because most have a technology transfer office that can assist. Institutions can help figure out funding to grow the idea into a company, but they are not the only source: there are venture capital sources, foundations, angel investors. "Have a patent filed. Contact your colleagues in industry. Publish and speak at meetings and work the crowd."

An important lesson: "An academic is rarely the best judge of IP value." **EBO**

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1. Adelman B. Opening up drug development to everyone. *Hematology Am Soc Hematol Edu Program.* 2013;2013:311-315.

2. American Society of Hematology. Statement from the American Society of Hematology on Congressional Budget Deal [press release]. Washington, DC: ASH Newsroom; December 18, 2013. http://www.hematology.org/News/2013/11941.aspx. Accessed January 2, 2014.

As Genomics Reveals Diversity of Lymphomas, Questions Arise on Diagnosis, Treatment, and Ethical Issues

Mary K. Caffrey

Treating lymphoma today starts with an understanding of what is being treated, and the revolution in genetic profiling lets clinicians do that with more precision than ever. But all those data can raise as many questions as they answer, while creating new ones in the ethical realm, according to the physicians who presented "Genomics in Hematology 101 for the Practicing Physician," an education session at the 55th American Society of Hematology (ASH) Annual Meeting and Exposition in New Orleans, held December 7-10, 2013.

The term "lymphoma" applies to at least 48 different diseases, and within each there can be considerable differences in how the cancer progresses and how patients respond to treatment.[1] There was a time when a patient's risk status at diagnosis was determined based on age, medical history, health status, and bloodwork or other tests. But genomics is rewriting that rulebook, according to presenters Sandeep S. Dave, MD, of Duke University; Richard F. Schlenk, MD, of University Hospital Ulm in Germany; and Stefan K. Bohlander, MD, of the University of Auckland, New Zealand.

What genomics is revealing, the presenters agreed, is the remarkable differences not only between different lymphoma states but *within* each; trying to assess a patient's risk level and treatment prospects without understanding his genetic profile would be akin to flying an airliner without instruments—one might survive but the ride would be bumpy.

Dave used examples from 3 diseases—diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), and chronic lymphocytic leukemia (CLL)—to highlight how the different genetic makeup of patients within each disease affected treatment. While DLBCL is a common disease, with 25,000 patients diagnosed and 10,000 deaths a year,[1] genomics has shown that DLBCL actually has 2 distinct subtypes with vastly different survival rates. Dave said high-throughput sequencing has recently revealed several hundred mutations, with each affecting only a small number of patients.

Burkitt's lymphoma affects far fewer patients (only about 2000), but it is aggressive, complex, and hard to diagnose, making it an important disease for researchers to understand genetically. In CLL, meanwhile, several gene mutations, including TP53, *NOTCH1*, and *SF3B1*, have been linked to poor prognosis. As these differences are better understood, Dave wrote in a companion paper to the session, it is becoming clear that many targeted agents will benefit only a relative handful of cases, making it essential to properly link drugs and patients.[1]

Understanding a patient's genetic profile doesn't end at diagnosis, according to Schlenk. In his review of genomic applications in acute myeloid leukemia (AML), he called for additional testing as the disease progresses, so clinicians can see how the genetic profile has changed and respond accordingly. This is especially important when a patient relapses, Schlenk said. As more becomes known about individual mutations and clinical trials are designed around increasingly distinct groups of patients, he predicted that international collaborations would need to form to attract enough patients for each genetic expression being studied.[2]

Bolander reviewed different levels and forms of genetic testing, and how much more scientists and clinicians can learn today. But with that knowledge comes responsibility, he said. Next-generation sequencing is producing huge amounts of data, but finding the "pearls"[3] comes only when clinicians know where to look. In the meantime, all those data must be stored and protected. Ethical guidelines are needed for gaining informed consent and for handling unexpected news that comes back with results.

"Current recommendations call for reporting only those findings with a high likelihood of causing disease—and for which intervention is possible," he said. These recommendations, however, "were done with human genetics in mind, not tumor samples." **EBO**

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1. Dave SS. Genomic stratification for the treatment of lymphomas. *Hematology Am Soc Hematol Edu Program.* 2013;2013:331-334.

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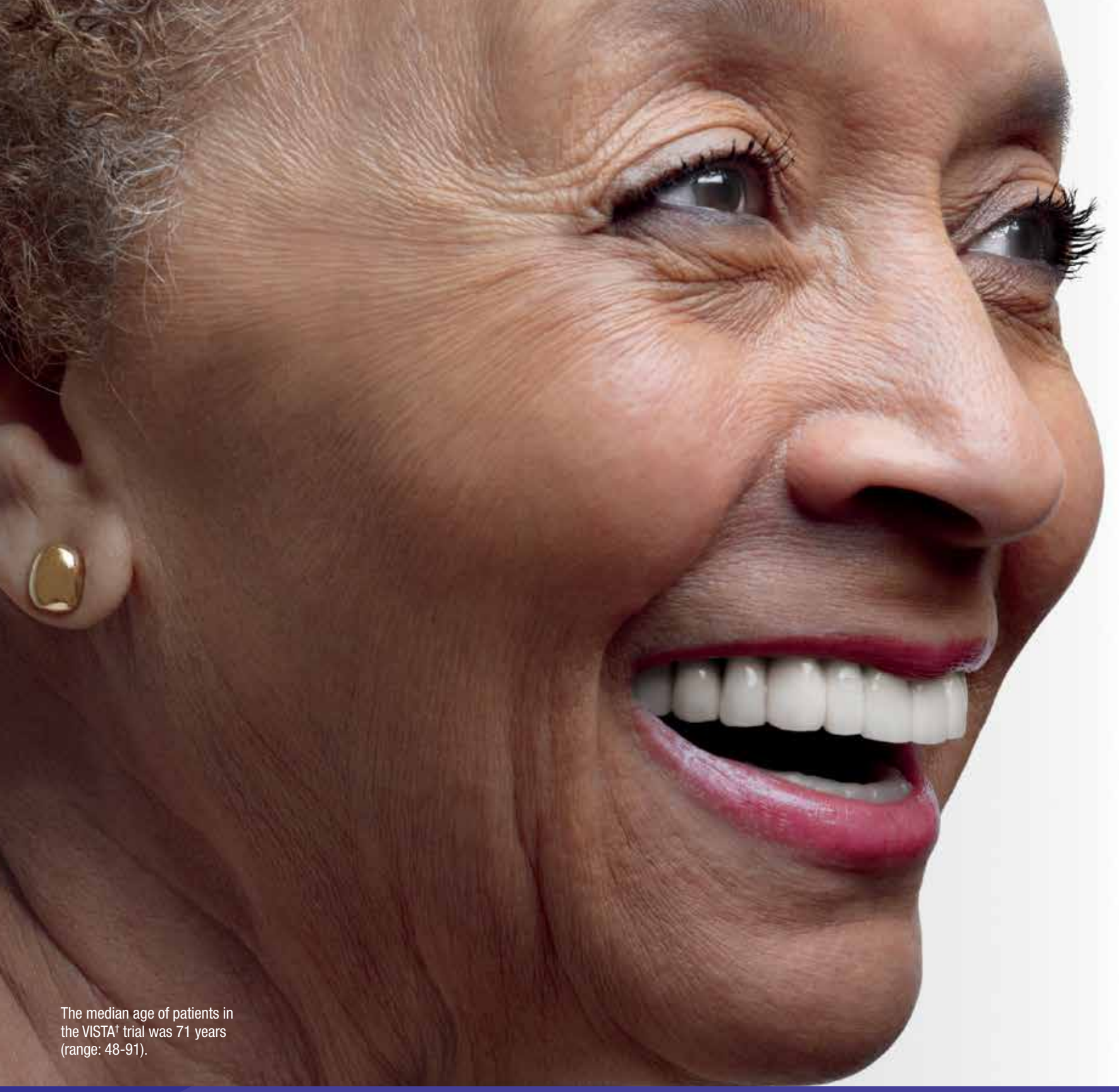


The median age of patients in the VISTA† trial was 71 years (range: 48-91).

Indication and Important Safety Information for VELCADE® (bortezomib)

INDICATION

VELCADE (bortezomib) is indicated for the treatment of patients with multiple myeloma.

CONTRAINDICATIONS

VELCADE is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol, including anaphylactic reactions. VELCADE is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of VELCADE.

WARNINGS, PRECAUTIONS, AND DRUG INTERACTIONS

- **Peripheral neuropathy:** Manage with dose modification or discontinuation. Patients with preexisting severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment.
- **Hypotension:** Use caution when treating patients taking antihypertensives, with a history of syncope, or with dehydration.
- **Cardiac toxicity:** Worsening of and development of cardiac failure have occurred. Closely monitor patients with existing heart disease or risk factors for heart disease.
- **Pulmonary toxicity:** Acute respiratory syndromes have occurred. Monitor closely for new or worsening symptoms.
- **Posterior reversible encephalopathy syndrome:** Consider MRI imaging for onset of visual or neurological symptoms; discontinue VELCADE if suspected.
- **Gastrointestinal toxicity:** Nausea, diarrhea, constipation, and vomiting may require use of antiemetic and antidiarrheal medications or fluid replacement.
- **Thrombocytopenia or Neutropenia:** Monitor complete blood counts regularly throughout treatment.
- **Tumor lysis syndrome:** Closely monitor patients with high tumor burden.
- **Hepatic toxicity:** Monitor hepatic enzymes during treatment.

In treating multiple myeloma

What is the value of VELCADE® (bortezomib)?

- Overall survival advantage
- Defined length of therapy
- Medication cost

IF YOU DEFINE VALUE AS AN OVERALL SURVIVAL ADVANTAGE:

VELCADE (bortezomib) combination delivered a >13-month overall survival advantage

- At 5-year median follow-up, VELCADE+MP* provided a median overall survival of 56.4 months vs 43.1 months with MP alone (HR=0.695 [95% CI, 0.57-0.85]; $p<0.05$)†
- At 3-year median follow-up, VELCADE+MP provided an overall survival advantage over MP that was not regained with subsequent therapies

IF YOU DEFINE VALUE AS DEFINED LENGTH OF THERAPY:

- Results achieved using VELCADE twice-weekly followed by weekly dosing for a median of 50 weeks (54 planned)[1]

IF YOU DEFINE VALUE AS MEDICATION COST:

- Medication cost is an important factor when considering overall drug spend. The Wholesale Acquisition Cost for VELCADE is $1568 per 3.5-mg vial as of January 2014
- When determining the value of a prescription drug regimen, it may be worth considering medication cost, length of therapy, and dosing regimens. This list is not all-inclusive; there are additional factors to consider when determining value for a given regimen

- **Embryo-fetal risk:** Women should avoid becoming pregnant while being treated with VELCADE. Advise pregnant women of potential embryo-fetal harm.
- Closely monitor patients receiving VELCADE in combination with strong **CYP3A4 inhibitors**. Avoid concomitant use of strong **CYP3A4 inducers**.

ADVERSE REACTIONS

Most commonly reported adverse reactions (incidence ≥20%) in clinical studies include nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia.

Please see Brief Summary for VELCADE on the next page of this advertisement.

For Reimbursement Assistance, call 1-866-VELCADE (835-2233), Option 2, or visit VELCADEHCP.com.

Reference: 1. Mateos M-V, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. *J Clin Oncol.* 2010;28(13):2259-2266.

*Melphalan+prednisone.

† **VISTA TRIAL:** a randomized, open-label, international phase 3 trial (N=682) evaluating the efficacy and safety of VELCADE administered intravenously in combination with MP vs MP in previously untreated multiple myeloma. The primary endpoint was TTP. Secondary endpoints were CR, ORR, PFS, and overall survival. At a prespecified interim analysis (median follow-up 16.3 months), VELCADE+MP resulted in significantly superior results for TTP (median 20.7 months with VELCADE+MP vs 15.0 months with MP [p=0.000002]), PFS, overall survival, and ORR. Further enrollment was halted and patients receiving MP were offered VELCADE in addition. Updated analysis was performed.

VELCADE®
(bortezomib) FOR INJECTION

VELCADE®
(bortezomib) FOR INJECTION

Brief Summary

INDICATIONS:

VELCADE® (bortezomib) for Injection is indicated for the treatment of patients with multiple myeloma. VELCADE for Injection is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

CONTRAINDICATIONS:

VELCADE is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol, including anaphylactic reactions. VELCADE is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of VELCADE.

WARNINGS AND PRECAUTIONS:

Peripheral Neuropathy: VELCADE treatment causes a peripheral neuropathy that is predominantly sensory; however, cases of severe sensory and motor peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain, or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including ≥Grade 3) during treatment with VELCADE. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. In the Phase 3 relapsed multiple myeloma trial comparing VELCADE subcutaneous vs intravenous, the incidence of Grade ≥2 peripheral neuropathy events was 24% for subcutaneous and 39% for intravenous. Grade ≥3 peripheral neuropathy occurred in 6% of patients in the subcutaneous treatment group, compared with 15% in the intravenous treatment group. Starting VELCADE subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy.

Patients experiencing new or worsening peripheral neuropathy during VELCADE therapy may require a decrease in the dose and/or a less dose-intense schedule. In the VELCADE vs dexamethasone phase 3 relapsed multiple myeloma study, improvement in or resolution of peripheral neuropathy was reported in 48% of patients with ≥Grade 2 peripheral neuropathy following dose adjustment or interruption. Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who had ≥Grade 3 peripheral neuropathy in the phase 2 multiple myeloma studies. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

Hypotension: The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 8%. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics.

Cardiac Toxicity: Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have occurred during VELCADE therapy, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing, heart disease should be closely monitored. In the relapsed multiple myeloma study of VELCADE vs dexamethasone, the incidence of any treatment-related cardiac disorder was 8% and 5% in the VELCADE and dexamethasone groups, respectively. The incidence of adverse reactions suggestive of heart failure (acute pulmonary edema, pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock) was ≤1% for each individual reaction in the VELCADE group. In the dexamethasone group, the incidence was ≤1% for cardiac failure and congestive cardiac failure; there were no reported reactions of acute pulmonary edema, pulmonary edema, or cardiogenic shock. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

Pulmonary Toxicity: Acute Respiratory Distress Syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology, such as pneumonitis, interstitial pneumonia, and lung infiltration have occurred in patients receiving VELCADE. Some of these events have been fatal. In a clinical trial, the first two patients given high-dose cytarabine (2 g/m^2 per day) by continuous infusion with daunorubicin and VELCADE for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy. There have been reports of pulmonary hypertension associated with VELCADE administration in the absence of left heart failure or significant pulmonary disease. In the event of new or worsening cardiopulmonary symptoms, consider interrupting VELCADE until a prompt, comprehensive, diagnostic evaluation is conducted.

Posterior Reversible Encephalopathy Syndrome (PRES): Posterior Reversible Encephalopathy Syndrome (PRES; formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS)) has occurred in patients receiving VELCADE. PRES is a rare, reversible, neurological disorder, which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis. In patients developing PRES, discontinue VELCADE. The safety of reinitiating VELCADE therapy in patients previously experiencing PRES is not known.

Gastrointestinal Toxicity: VELCADE treatment can cause nausea, diarrhea, constipation, and vomiting, sometimes requiring use of antiemetic and antidiarrheal medications. Ileus can occur. Fluid and electrolyte replacement should be administered to prevent dehydration. Interrupt VELCADE for severe symptoms.

Thrombocytopenia/Neutropenia: VELCADE is associated with thrombocytopenia and neutropenia that follow a cyclical pattern, with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of the subsequent cycle. The cyclical pattern of platelet and neutrophil decreases and recovery remained consistent over the 8 cycles of twice-weekly dosing, and there was no evidence of cumulative thrombocytopenia or neutropenia. The mean platelet count nadir measured was approximately 40% of baseline. The severity of thrombocytopenia was related to pretreatment platelet count. In the relapsed multiple myeloma study of VELCADE vs dexamethasone, the incidence of bleeding (≥Grade 3) was 2% on the VELCADE arm and <1% on the dexamethasone arm. Complete blood counts (CBC) should be monitored frequently during treatment with VELCADE. Platelet counts should be monitored prior to each dose of VELCADE. Patients experiencing thrombocytopenia may require change in the dose and schedule of VELCADE. Gastrointestinal and intracerebral hemorrhage has been reported in association with VELCADE. Transfusions may be considered.

Tumor Lysis Syndrome: Tumor lysis syndrome has been reported with VELCADE therapy. Patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor patients closely and take appropriate precautions.

Hepatic Toxicity: Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include hepatitis, increases in liver enzymes, and hyperbilirubinemia. Interrupt VELCADE therapy to assess reversibility. There is limited re-challenge information in these patients.

Embryo-fetal: Pregnancy Category D. Women of reproductive potential should avoid becoming pregnant while being treated with VELCADE. Bortezomib administered to rabbits during organogenesis at a dose approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area caused post-implantation loss and a decreased number of live fetuses.

ADVERSE EVENT DATA:

Safety data from phase 2 and 3 studies of single-agent VELCADE 1.3 mg/m^2/dose administered intravenously twice weekly for 2 weeks followed by a 10-day rest period in 1163 patients with previously-treated multiple myeloma (N=1008) and previously-treated mantle cell lymphoma (N=155) were integrated and tabulated. In these studies, the safety profile of VELCADE was similar in patients with multiple myeloma and mantle cell lymphoma.

In the integrated analysis, the most commonly reported (≥10%) adverse reactions were nausea (49%), diarrhea NOS (46%), fatigue (41%), peripheral neuropathies NEC (38%), thrombocytopenia (32%), vomiting NOS (28%), constipation (25%), pyrexia (21%), anorexia (20%), anemia NOS (18%), headache NOS (15%), neutropenia (15%), rash NOS (13%), paresthesia (13%), dizziness (excl vertigo 11%), and weakness (11%). Eleven percent (11%) of patients experienced at least 1 episode of ≥Grade 4 toxicity, most commonly thrombocytopenia (4%) and neutropenia (2%). A total of 26% of patients experienced a serious adverse reaction during the studies. The most commonly reported serious adverse reactions included diarrhea, vomiting, and pyrexia (3% each), nausea, dehydration, and thrombocytopenia (2% each), and pneumonia, dyspnea, peripheral neuropathies NEC, and herpes zoster (1% each).

In the phase 3 VELCADE+melphalan and prednisone study in previously untreated multiple myeloma, the safety profile of VELCADE administered intravenously in combination with melphalan/prednisone is consistent with the known safety profiles of both VELCADE and melphalan/prednisone. The most commonly reported adverse reactions in this study (VELCADE+melphalan/prednisone vs melphalan/prednisone) were thrombocytopenia (48% vs 42%), neutropenia (47% vs 42%), peripheral neuropathy (46% vs 1%), nausea (39% vs 21%), diarrhea (35% vs 6%), neuralgia (34% vs <1%), anemia (32% vs 46%), leukopenia (32% vs 28%), vomiting (26% vs 12%), fatigue (25% vs 14%), lymphopenia (23% vs 15%), constipation (23% vs 4%), anorexia (19% vs 6%), asthenia (16% vs 7%), pyrexia (16% vs 6%), paresthesia (12% vs 1%), herpes zoster (11% vs 3%), rash (11% vs 2%), abdominal pain upper (10% vs 6%), and insomnia (10% vs 6%).

In the phase 3 VELCADE subcutaneous vs intravenous study in relapsed multiple myeloma, safety data were similar between the two treatment groups. The most commonly reported adverse reactions in this study were peripheral neuropathy NEC (37% vs 50%), thrombocytopenia (30% vs 34%), neutropenia (23% vs 27%), neuralgia (23% vs 23%), anemia (19% vs 23%), diarrhea (19% vs 28%), leukopenia (18% vs 20%), nausea (16% vs 14%), pyrexia (12% vs 8%), vomiting (9% vs 11%), asthenia (7% vs 16%), and fatigue (7% vs 15%). The incidence of serious adverse reactions was similar for the subcutaneous treatment group (20%) and the intravenous treatment group (19%). The most commonly reported SARs were pneumonia and pyrexia (2% each) in the subcutaneous treatment group and pneumonia, diarrhea, and peripheral sensory neuropathy (3% each) in the intravenous treatment group.

DRUG INTERACTIONS:

Bortezomib is a substrate of cytochrome P450 enzyme 3A4, 2C19 and 1A2. Co-administration of ketoconazole, a strong CYP3A4 inhibitor, increased the exposure of bortezomib by 35% in 12 patients. Monitor patients for signs of bortezomib toxicity and consider a bortezomib dose reduction if bortezomib must be given in combination with strong CYP3A4 inhibitors (eg, ketoconazole, ritonavir). Co-administration of omeprazole, a strong inhibitor of CYP2C19, had no effect on the exposure of bortezomib in 17 patients. Co-administration of rifampin, a strong CYP3A4 inducer, is expected to decrease the exposure of bortezomib by at least 45%. Because the drug interaction study (n=6) was not designed to exert the maximum effect of rifampin on bortezomib PK, decreases greater than 45% may occur. Efficacy may be reduced when VELCADE is used in combination with strong CYP3A4 inducers; therefore, concomitant use of strong CYP3A4 inducers is not recommended in patients receiving VELCADE. St. John's wort *(Hypericum perforatum)* may decrease bortezomib exposure unpredictably and should be avoided. Co-administration of dexamethasone, a weak CYP3A4 inducer, had no effect on the exposure of bortezomib in 7 patients. Co-administration of melphalan-prednisone increased the exposure of bortezomib by 17% in 21 patients. However, this increase is unlikely to be clinically relevant.

USE IN SPECIFIC POPULATIONS:

Nursing Mothers: It is not known whether bortezomib 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 VELCADE, 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 VELCADE in children has not been established.

Geriatric Use: No overall differences in safety or effectiveness were observed between patients ≥age 65 and younger patients receiving VELCADE; but greater sensitivity of some older individuals cannot be ruled out.

Patients with Renal Impairment: The pharmacokinetics of VELCADE are not influenced by the degree of renal impairment. Therefore, dosing adjustments of VELCADE are not necessary for patients with renal insufficiency. Since dialysis may reduce VELCADE concentrations, VELCADE should be administered after the dialysis procedure. For information concerning dosing of melphalan in patients with renal impairment, see manufacturer's prescribing information.

Patients with Hepatic Impairment: The exposure of bortezomib is increased in patients with moderate and severe hepatic impairment. Starting dose should be reduced in those patients.

Patients with Diabetes: During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving VELCADE treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medication.

Please see full Prescribing Information for VELCADE at VELCADEHCP.com.

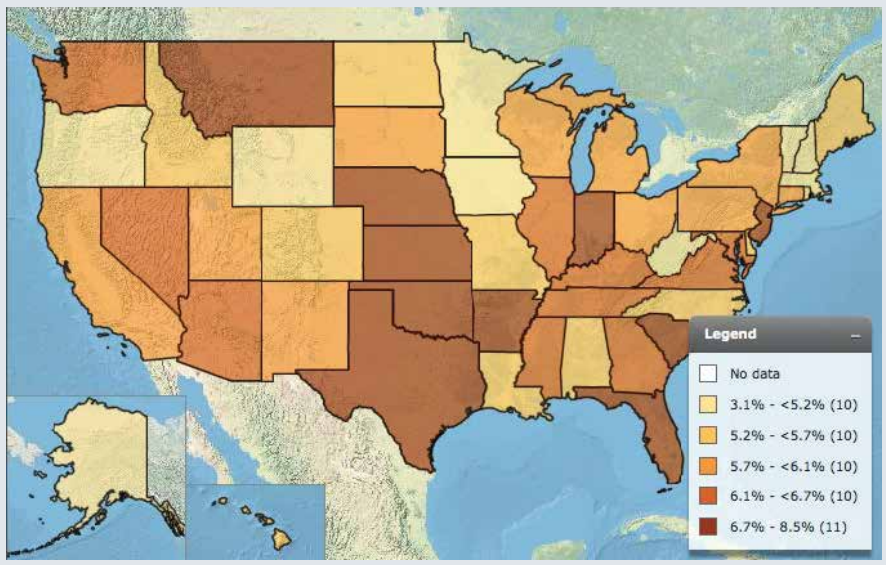
Takeda MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

V-12-0306a 1/14

Payment Reform
(continued from cover)

Researchers from the Dartmouth Institute found important differences among patients being treated within the final 2 weeks of life with active chemotherapy (**Figure 1**),[4] which has important implications for the cost of care.

Figure 1. Variation Across U.S. in Percent of Patients Receiving Chemotherapy in Last 2 Weeks of Their Life



Source: Dartmouth Institute for Health Policy and Clinical Practice.

The Growth of Oncology Clinical Pathways

The move from oncology practice guidelines to clinical pathways in the commercial sector is under way, judging from the deals being announced and consummated. Vendors like McKesson (which owns US Oncology), Via Oncology, and Cardinal Health have been active for several years in the clinical pathways arena. Twenty-eight percent of health plans responding to a 2013 survey indicated that they currently utilize oncology clinical pathways. Another 50% indicated that they would do so within 3 years.[7] According to McKesson, up to 1500 oncologists are using its oncology pathways, and Aetna has been a customer for its clinical pathways for about 7 years.

The reason for this move toward clinical pathways may be that the treatment options listed by today's practice guidelines are too broad, and these guideline recommendations are not usually based on adequate evidence (see **Highlight Box**). As an example, Bruce A. Feinberg, DO, chief medical officer of Cardinal Health Specialty Solutions, reported in the *National Cancer Institute Bulletin* that of the 16 possible ways to treat metastatic HER2-negative, estrogen-receptor negative breast cancer, "most of them will never be tested head-to-head to determine which are the most effective, least toxic, and least costly."[8] The idea is to not to wring *all* variation out of oncology practice, but, according to Via Oncology, to strive for 80% adherence to any single pathway.[8]

Matt Brow

In general, oncology clinical pathways are programs that clinicians can access in real time, during consultations with the patient. For example, McKesson's "Clear Value Plus" pathway product can connect and work automatically with any electronic health record (EHR).

As more genomic information is deciphered on a patient-by-patient basis, it makes sense that oncology pathways may become even more popular, to help guide clinicians in their treatment of individual patients with different genetic tumor characteristics. In this case, the number of options in a specific pathway will narrow further to those known to be most effective for a patient with a particular tumor genotype. This can only occur with more evidence-based medicine and comparative effectiveness research.

Even traditional providers of oncology practice guidelines, the professional associations, have started to look toward clinical pathways. Recently, McKesson has partnered with the National Comprehensive Cancer Network (NCCN), whose guidelines drive government reimbursement. "McKesson has partnered in the last year with NCCN to deliver clinical decision support, including NCCN guidelines and Value Pathways with our Clear Value Plus product," said Matt Brow, McKesson's vice president for business development and public policy. "With ready access to NCCN guidelines and Value Pathways Powered by NCCN in the physician's work flow, physicians and practices have more ways to demonstrate quality when working with payers." He added that payers would gain more value in this setting if use of oncology clinical pathways means that clinicians are always "green lighted" through the prior authorization system when on pathway.

Getting Medicare's Ear

A busy oncology practice may have commercial, Medicare, and Medicaid patients. Today, there is little standardization, and this is a difficult problem for community oncologists. As pathways become more popular, there's a recognition that practices will face administrative challenges if every payer works off a different clinical pathway type. Therefore, it would be preferable to have a common pathway format and approved approach. But so far, the biggest payer of all, the Centers for Medicare & Medicaid Services (CMS), has not moved in this direction.

In 2011, Medicare spent $34.4 billion for cancer care.[9] This represents 10% of its total fee-for-service payments for the year. As **Figure 2** shows, the majority of patients being diagnosed with cancer are Medicare beneficiaries[9]; some estimate that 65% of all patients with cancer may be covered by Medicare by 2020. It is well known among payers that commercial plans generally follow Medicare's lead on reimbursement and coverage, in part to reduce the confusion surrounding distinct and separate policies for many technologies.

"Most of the progress in reimbursement around clinical pathway development and adoption has been on the private payer side," according to Brow. As McKesson supports the US Oncology Network, its influence extends throughout this oncology network. "But the federal market is a bit behind the times," Brow said. "We've been pushing CMS to do this for years," he said, "but they had been more focused on primary care."

Finally, CMS is reviewing a proposal by McKesson and NCCN to utilize their oncology clinical pathways. If the proposal is accepted, McKesson believes that CMS will roll it out as a pilot project in certain oncology practices and hospital settings sometime in 2014. "We may be able to work on a framework in the first quarter, and start organizing the pilot perhaps 6 months later," Brow said. If the pilot is successful after 2 or 3 years, "We hope Medicare will look to roll it out more broadly."

McKesson and others are working with CMS to develop a structure for Medicare value-based reimbursement that can be used across oncology practices, using the clinical pathways. Brow also suspects that, if its shared savings programs in primary care are successful, CMS will shift this structure to work with specialty care, like oncology and cardiology, in an effort to drive efficiency and cost-effectiveness in these and other specialties. "We think that, for the most part, the oncologist acts like a primary care provider (or at least a principal care provider) for the patient with cancer. A narrower clinical focus may help yield more savings than seen with the primary care model," he said.

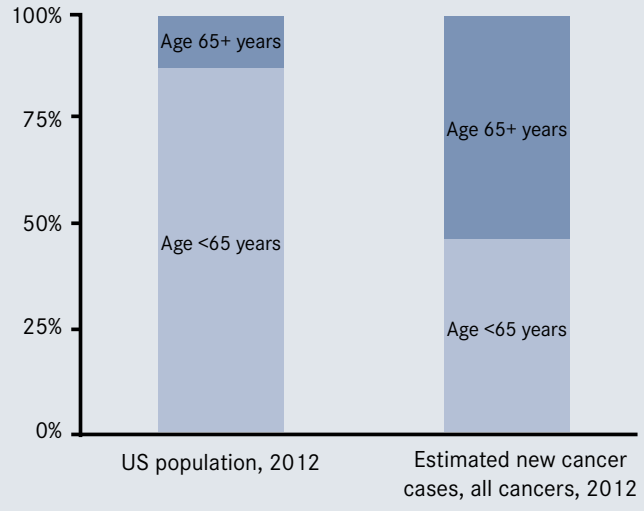
Aligning Incentives to Use Clinical Pathways

By following clinical pathways, or practice guidelines for that matter, under historical fee-for-service reimbursement structures, community oncologists may be jeopardizing the health of their own group practices, based on the type of therapy, where it is administered, and how it is reimbursed. If one considers the usual prompt pay discount of 2% on chemotherapy, and generally a 2-quarter lag in reimbursements, Medicare's reimbursement formula of average sales price (ASP) + 6% makes it difficult to break even if chemotherapy is administered in the physician's office.[2] The effect

Highlight Box: Oncology Clinical Pathways Versus Practice Guidelines

Practice guidelines are broadly considered to contain all treatment options that may produce improved outcomes. Clinical pathways offer narrower choices. This is the core difference, according to Matt Brow, vice president, business development & public policy, McKesson. "You will have a guideline that encompasses everything that may be successful in a specific circumstance. That may result in 20 or 30 good choices, some of these may be better than others," he said. To construct the clinical pathway, clinicians and pharmacists will determine which approaches are better from an efficacy perspective, driven first by randomized controlled trial evidence. "Sometimes there are no clearly superior choices," Brow said. "They will then look at side effect/toxicity profile, focusing on the least toxic choice."

Figure 2. Medicare Beneficiaries Over Age 65 Years Account for 54% of All New Cancer Cases



Source: Stockdale 2013.[9]

of the federal budget sequester has been to lower reimbursement to ASP + 4.2%, forcing many practices to either take a financial loss or direct patients to receive care at an infusion center or hospital outpatient facility, which costs taxpayers more than if the care took place in a community practice.[2,10]

"A number of providers could be financially penalized for doing the right thing. If you consistently choose the right drugs," said Brow, "you could lose money on your business—if the reimbursement system is set up so that using a more expensive drug can be more profitable, or a loser than using a less-expensive drug. The solution is to align across the payment spectrum for efficacy first, safety second, and cost-effectiveness third," he stated. The incentives in the system, especially on the fee-for-service commercial side, are currently to use more expensive products, services, and drugs, and receive more in reimbursements. Even in Medicare, where hospitals get bundled part A payments and don't receive additional fees for more diagnostic testing, for example, the hospitals don't receive financial bonuses for doing the right thing, such as improving readmission rates.

Brow noted, "Drugs account for about 25% to 35% of the cost of cancer care. The hospital is the greatest cost center. Therefore, we shouldn't focus on drugs alone. It is not productive to put blinders on and forget that the other 60% exists; all of these costs can be effectively managed." Clinical pathways must therefore be incentivized across the cancer care spectrum to produce their most beneficial improvements, both in care and expenditures.

A 2013 study pointed out the potential savings from the use of an oncology pathways program. Using Cardinal Health's pathways solution, CareFirst Blue Cross and Blue Shield found that total costs for cancer care were 15% lower than anticipated costs (without the use of oncology clinical pathways). Inpatient admissions were projected to be 7% lower using the oncology pathways, a major contributor to cost savings.[11]

However, the question of whether clinical pathways improve care, through reduced variation in oncology care methods, has not been answered. Feinberg, at Cardinal Health, had stated previously that this is "largely an act of faith… You have to look for behavioral changes that you believe represent better care."[8] There's hope that through the use of an oncology pathway system, one can support the use of evidence-based interventions, and these proxies for quality care may lead to real, documented proof that more personalized oncology care guidelines do translate to better outcomes. **EBO**

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Patient Navigators

(continued from cover)

move impediments that limit the access to care in minority populations and can improve outcomes."[3] A survey of impoverished African American women diagnosed and treated at a public hospital for breast cancer found that their patient navigation needs began with improving their access to quality care, but evolved to include addressing their emotional and practical problems, as well as family concerns.[4] The best results came from a sustained relationship with the patient, from diagnosis into long-term survivorship.[4]

The concept of training patient navigators was created by Harold P. Freeman, MD, of Harlem Hospital Center in New York City. Freeman, as president of the American Cancer Society, in 1989 chaired public meetings to hear from impoverished cancer patients in all 50 states. Freeman wrote that the hearings revealed how "Poor people experience substantial barriers when seeking timely screening, diagnosis, and treatment of cancer."[5]

Freeman founded the nation's first patient navigation program in 1990 at Harlem Hospital to address the problems uncovered by patient testimony. In a widely cited 2006 paper,[5] he reported that patient navigators helped improve the 5-year survival rate among poor women treated at the hospital, about half of whom lacked health insurance, due to the assistance of patient navigators. The 5-year survival rate for breast cancer patients at Harlem Hospital Center, prior to the patient navigation program, was 39%, but that figure rose to 70% for a demographically similar group of patients aided by patient navigators. Freeman attributed the results to 2 factors: first, effective public education efforts increased the number of women receiving affordable mammograms; second, the navigators' work in aiding patients in overcoming barriers to prompt, appropriate treatment, as determined by the screening results.[5]

Navigating Survivorship

The 2005 IOM report recognized survivorship as "a distinct phase of cancer care."[2] The recommendations stressed that every cancer survivor requires a "survivorship care plan," understandable to the patient, to coordinate care and also advise the survivor about support groups and similar resources.[2]

Ellen Stovall, senior health policy advisor for the National Coalition for Cancer Survivorship and a 3-time cancer survivor, said the services of a skilled navigator are required most when the patient is receiving the diagnosis.

"The diagnosis slams you against the wall," she said. "The most important decision is the first round of treatment. Before a person decides that, they need a patient navigator to demystify what will happen and help them articulate their goals so the patient can navigate his or her own cancer treatment. If you are diagnosed with acute leukemia, you need to start treatment quickly, but if you have a solid tumor, you likely have weeks to decide what to do. But the reality is, people usually decide in the first 40-minute extended office visit. Most people would take longer to decide on buying a car or a house."

Stovall said there are no agreed-upon core competencies for a "patient naviga-

tor," but notes some hospitals advertise the service.

"The job definition isn't clear but the process is helping people with decision making, coordination of care, working with local agencies, finding the right referrals, helping special populations," she said. "A hospital I know that is very well ranked and respected advertises one of the best navigator programs around, but people working there tell me the navigator mostly gets the person through the billing department. In some places, the patient navigator is in charge of coordination of care, with the work relegated sometimes to people who are not trained for it, but sometimes to people who are overqualified. The term is used very broadly."

The LIVESTRONG Foundation offers wide-ranging navigator services, at no charge, online, by telephone, and in person. Its website offers information in lay terms in categories with titles such as just diagnosed, preparing yourself, and insurance/financial assistance.[6] The LIVESTRONG Guidebook for the newly diagnosed patient includes practical advice like lining up help with driving, cooking, and other tasks.[7]

"Nobody should be alone when they have cancer," said Sarah Gomez Wauters, LIVESTRONG outreach coordinator. "Cancer throws a person into a new chapter of life. People don't know everything that comes along with the diagnosis. Nobody is thinking if you have cancer you might not be able to have children, depending upon your diagnosis. You think you are covered, until you find out not everything is paid for. If you are the breadwinner, you might be unable to work, and that income is gone. No diagnosis is the same, no journey is the same, so we provide individualized care."

Rose Gerber, now director of communications and patient advocacy for the Community Oncology Alliance (COA), was thunderstruck in 2003 when, at age 39 years with 2 young children, she received her diagnosis of early onset breast cancer with cancer in the lymph nodes, large tumor, HER2+ and BRCA abnormality. Her ultimately successful treatment was a grueling regimen of intravenous chemotherapy and radiation, followed by participation in a 52-week clinical trial of Herceptin, Zoladex injections for 4 years, and Tamoxifen for 5 years. There was no system in place for coordinating care with the dozen specialists, primary care physicians, and complementary care providers she saw over the years, but the informal monitoring was good.

"About 5 years after my diagnosis, I was having a routine exam with my ophthalmologist. He made a note about my cancer treatment," recalled Gerber. "The first thing he said to me after the examination was 'The good news is there is no metastasis to the eye.' That almost knocked me over. I didn't go to the ophthalmologist because I was worried about cancer. That was the first time I learned my cancer could metastasize to the eye."

Anne Slam, administrator for 23 years at Eastern Connecticut Hematology and Oncology where Gerber has been treated since her diagnosis, said coordinating care and assisting patients in finding help paying for care were not part of patient care years ago, but are now.

"There are more treatments, better treatments, and patients are now treated for years, which is all good but has its own challenges," Slam said. "People need help. A lot of it is time consuming, and we can't get paid for everything all the time, but we do it." **EBO**

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Washington State
(continued from cover)

put it among a handful of states receiving good reviews in the ACA rollout.[5]

Data from 2010 show Washington's cancer story is mixed. It is among the top 10 states in the nation for cancer incidence, at 472.2 cases per 100,000, compared with 445.5 nationally. But its death rates are lower: 169.6 per 100,000, compared with 171.8 nationwide, according to the Centers for Disease Control and Prevention (CDC). Except for slightly elevated rates of melanoma, the types of cancer seen in Washington mirror the nation's (see **Figure**).[6]

In 2001, Washington formed the Comprehensive Cancer Control Partnership and has a statewide blueprint, the Washington State Comprehensive Cancer Control Plan, which is updated every 4 years. Prevention and screening are emphasized, and both are a natural for a culture with greater focus on fitness and health than some parts of the country. Still, Washington state has issues with disparities; low-income pockets suffer higher rates of cancer, and tribal and rural health merited special notice throughout the Health Care Authority's recent federal grant application.[2] Tobacco use is common among lower-income groups, and Native Americans suffer high rates of lung cancer, for example.[7]

There's a new concern, too. A reorganization of state funding for healthcare programs generally will mean a phaseout of state funding to Washington's Breast, Cervical and Colon Health Program (BCCHP), which through the end of 2013 provided free screening for these diseases to low-income residents. Women diagnosed with cancers were moved immediately into treatment.[8]

As of January 1, 2014, Washington's BCCHP is still screening some patients, but the potential for gaps exists, according to Megan Celedonia, program manager. Those screened and diagnosed with cancer no longer have access to the companion treatment program, and BCCHP can no longer screen patients with insurance. About 75% of the program's former target population will be eligible for Medicaid under ACA. The rest would have to sign up for subsidized coverage, but Celedonia cautions that not all will be eligible, and some will not have funds to enroll.

"We can't expect that all will enroll on to insurance programs immediately," Celedonia said. "We expect that our clients will continue to need our program. Some will be diagnosed and will need access to treatment. We need safety net services."

A Transition to Value-Based Care

Is the phaseout of the screening program an anomaly in a state that, from all other appearances, puts a high value on healthcare? Or is this what the transition of healthcare reform is all about: Moving the population away from the mind-set of safety net "services" into one in which *being insured is the safety net*?

What's evident is that Washington state is in the process of embracing value-based care, of which the expansion of coverage under the ACA is merely a part. In December, Washington's Health Care Authority, which runs Medicaid and other state healthcare programs, unveiled its State Innovation Plan,[2] a venture that involved multiple agencies and Governor Inslee's office. Among its goals, it seeks to:

- move 80% of Medicaid spending into outcome-based models[7]
- create regional "accountable communities of health," for measuring clinical and community factors that affect Medicaid populations
- better integrate physical and behavioral health
- promote better healthcare IT. For cancer, this will include basic items like ensuring that tumor data from Washington's rural counties are reported to the National Cancer Institute's Surveillance, Epidemiology and End Results program. A map for 2010 had no data from the eastern counties

In rolling out their plan, officials from Washington's Health Care Authority vowed that whatever the result of their pursuit of the grant, the commitment to value-based healthcare is here to stay. "We're getting geared up for implementation efforts with or without federal dollars arriving," Nathan Johnson, director of healthcare policy at the HCA, told a Puget Sound publication.[9]

Some insurers like Group Health Cooperative, which accounts for about 10% of the state's market share, already take value-based practices quite seriously; Melinda Hews, executive director, health insurance exchanges, at Group Health, said all members, regardless of how they access Group health coverage, "receive care through a capitated medical home model." (E-mail communication, January 2014.)

In the first year of benefit design, not all insurers are as advanced, but Hews expects this will change. "I think this will mature in subsequent years as new pay-for-performance models of provi-

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der contracting gain traction and benefits may be designed differently to support that," Hews said.[10]

Commitment to Clinical Pathways

If Washington state's efforts take hold, more cancer care will be delivered the way it is within the Group Health Cooperative, which covers 600,000 people in Washington and Idaho.[10] The cooperative's use of clinical pathways has a national reputation, one that Eric Chen, MD, PhD, a medical oncologist who practices within the plan, appreciates not only for its ability to deliver good care but for his ability to help his patients understand their disease.

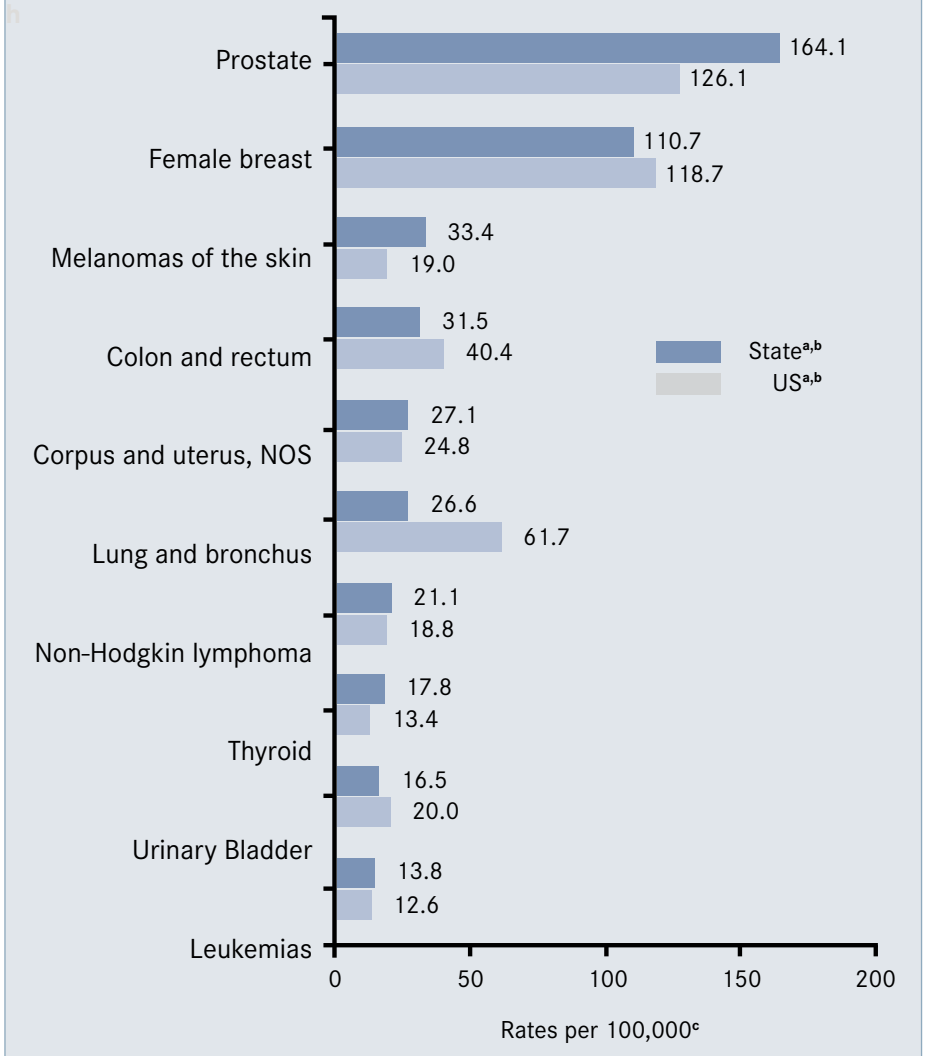
The pathways approach created evidence-based treatment approaches that go beyond therapies that are approved by the US Food and Drug Administration (FDA) or within guidelines of the National Comprehensive Cancer Network (NCCN). Pathways prevent outliers from allowing poor quality care or driving up costs unnecessarily.

"If there is a new standard of care, we can implement something so that everyone does the same thing," Chen said. "It's very easy for everyone to get on the same page." He said pathways help doctors and payers overcome the "inertia" that works against doing things differently.

Chen has spent his entire post training career practicing medicine this way; to him, it allows the best therapies to rise to the top without external pressure. He knows, however, that not everyone agrees.

"There are people who criticize pathways; they say, 'that's robot medicine.' There's a lot in medicine that we can do by algorithm, but the algorithm can only carry you so far. It takes a human being to make the decisions," Chen said.

Figure. New Cancer Case (Incidence) Rates—Washington Versus United States, 2010, Male and Female



[a]Data are from selected statewide and metropolitan area cancer registries that meet the data quality criteria for all invasive cancer sites combined. See registry-specific data quality information. Rates cover approximately 97% of the US population.
[b]Excludes basal and squamous cell carcinomas of the skin except when these occur on the skin of the genital organs, and in situ cancers except urinary bladder.
[c]Rates are age-adjusted to the 2000 US standard population (19 age groups – Census P25–1130).
NOS indicates not otherwise specified.

Creating Value in Being Covered

Getting people to see the value proposition of being insured is going to take time, and it's going to take education, according to Michael Marchand, communications director at the Washington State Health Benefit Exchange. Marchand spoke to *Evidence-Based Oncology* last fall, after surveying Washington's experience compared with the first rocky weeks of the federal website, healthcare.gov. He attributes Washington's early success to strong bipartisan leadership that recognized the state would be best served if it tailored an exchange to its unique qualities. Given its workforce, that meant creating a user experience that didn't feel like government.

Marchand said Washington's exchange creators made a key decision to reject a recommendation from a technology conference—attended by all the major exchanges including healthcare.gov—to require users to register before they could browse for coverage. "That single recommendation drove a lot of the decision making for healthcare.gov," Marchand said. "We chose to ignore it… We wanted to set up a consumer experience more like Amazon.com."

In the first few weeks, Washington saw 17% of the purchasing among consumers aged 55 to 64 years, which did not surprise Marchand at all. "These are people who have been insured at some other point in their life. They probably need it, so they are the quickest to react," he said. Many of the so-called "young invincibles" will wait until the last minute before penalties begin this spring, because that's "human behavior."

"Insurance isn't top of mind—until you get sick. Then, it's important," Marchand said.

To change that mind-set, Washington state's exchange staff meet with small businesses to link healthcare reform to economic health. Being insured goes hand-in-hand with being productive, Marchand said; there's nothing wrong with getting insurance at your job, but if that's the only place you can get it, it limits self-employment and entrepreneurship. Washington state is creating a system that will allow its "start-up" mentality to flourish, he said, because small businesses will have a way to cover employees that did not previously exist.

Washington state's strong start has been helped by community support, Marchand said. Ten lead organizations, 1400 in-person assisters (or navigators), 2000 agents and brokers, and scores of customer service personnel have all done their part to get the process off the ground, he said. "I have never seen anything like it," said Marchand, who has worked in healthcare for a long time.

"People understand that if you have healthcare, it helps with everything. Everyone wins when people are insured," he said. "We all benefit as a state, and as a society if people can have healthcare." **EBO**

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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 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)*]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [*see Warnings and Precautions (5.5)*]

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.

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

There are no adequate and well-controlled studies of GRANIX in pregnant women. In an embryofetal developmental study, treatment of pregnant rabbits with tbo-filgrastim resulted in adverse embryofetal findings, including increased spontaneous abortion and fetal malformations at a maternally toxic dose. GRANIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In the 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 ($AUC_{0\text{-}24}$) 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-40188 January 2014

This brief summary is based on TBO-003 GRANIX full Prescribing Information.

GRANIX™
(TBO-FILGRASTIM)
Injection

Take a bite out of G-CSF acquisition costs*

GRANIX™ is another option in short-acting G-CSF therapy

GRANIX™ is an option for hospitals and payers to consider when determining health system budgets

- **FDA approved through the rigorous BLA† process**
- **Teva's short-acting G-CSF was first introduced in Europe in 2008 and is available in 42 countries‡[1]**
- **GRANIX J Code: J 1446-Injection, tbo-filgrastim, 5 micrograms, effective January 1, 2014**

†Biologics License Application.

‡As of February 2014.

*Based on wholesale acquisition cost (WAC) of all short-acting G-CSF products as of November 11, 2013. WAC represents published catalogue or list prices and may not represent actual transactional prices. Please contact your supplier for actual prices.

Indication

- 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.
- **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.

Reference: 1. Data on file. Teva Pharmaceuticals: Filgrastim MA Approvals Worldwide. February 2014.

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