Bridging the gap between payer and provider perspectives

THE AMERICAN JOURNAL OF MANAGED CARE®

#1 IN CITATIONS & IMPACT FACTOR

Volume 18
Special Issue 3

Evidence-Based Oncology

Best Practice

Forging a Pathway to Quality Cancer Care

UPMC Oncologists: Pioneers in the Clinical Pathways Movement

Kim Farina, PhD

Peter Ellis, MD

Kathy Lokay

With 180 oncologists practicing at more than 30 locations, UPMC Cancer Centers is one of the largest networks of cancer specialists in the country. In the early 2000s, the oncologists at UPMC recognized the importance of consistency and quality of care and the difficulties of ensuring a uniform level of care across their large distributed network. At the same time, they found themselves caught in the crosshairs of healthcare plans' efforts to ratchet down the rising costs of cancer care. Together, these factors drove UPMC oncologists to develop clinical cancer pathways. Clinical pathways are treatment plans that lead physicians to 1 preferred treatment for a given state and stage of disease.[1] Pathway programs are believed to be a cost-effective way to provide evidence-based patient care.[2,3] Over the past several years, UPMC has continued to use, improve, and expand its pathway program. For UPMC, clinical pathways are a way to ensure that all patients going to any UPMC location get the same care.

Prompted by its success and a growing interest in pathways among the broader oncology community, UPMC commercialized its program. This move made its well-founded pathways,

(continued on page SP116)

Practice Management

Is Provenge Angst a Symbol or Symptom of the Times?

Dawn G. Holcombe, MBA, FAMCPE, ACHE

Much has been said and written about the circumstances surrounding the launch of Dendreon's innovation in cancer treatment, Provenge, a novel immunotherapeutic treatment for end-stage prostate cancer. In the months following the initial launch, capacity limitations were said to have constricted the potential uptake of the treatment in the medical community, masking the balance between sales and projected sales. As time went on and capacity issues were resolved, a Q code was assigned in July 2011 to the treatment, which improved billing issues, and expectations remained high among investors for product uptake.

Dawn G. Holcombe, MBA, FAMCPE, ACHE

(continued on page SP108)

Commentary

Value-Based Reimbursement in Oncology

Getting "On Pathway"?

Michael Kolodziej, MD; and
J. Russell Hoverman, MD, PhD

The rising cost of healthcare is a topic of constant discussion and equally constant consternation. A lot of money is spent on healthcare in America, far more than in any other Western country, and over time, there has been tremendous inflation in this spending, particularly when indexed against the GDP.[1] Oncology seems a particularly prominent passenger on this runaway train. Although oncology spending in both the commercial and Medicare sectors represents less than 10% of the total healthcare spend,[2] several big-ticket items bring constant attention to this specialty. And why not, with immunotherapy costing $100,000 per course and oral targeted agents costing $5000 to $10,000 per month? These mind-boggling price tags seem out of reach for the average patient.

Michael Kolodziej, MD; and
J. Russell Hoverman, MD, PhD

A major reason for the concern over the cost of these agents is the perceived lack of value. The clinical trials that have led to the approval of these agents often employ end points, or outcomes, that address only part of the value assessment patients must make. High cost may interfere with living longer or better regardless of disease-free survival or disease stability.

The ability to rank "relative values" associated with our therapeutic

(continued on page SP124)

Also in this issue...

AJMC TV

Susan Urba, MD, Professor, Department of Internal Medicine, University of Michigan Comprehensive Cancer Center, Discusses Cost Concerns for Treatment of Chemotherapy-Induced Nausea

Ravi Vij, MD, Associate Professor of Medicine, Washington University School of Medicine, Discusses Benefits/Efficacy of Carfilzomib and Revlimid

Intellisphere
Managed Markets Group

AJMC.com

A supplement to
The American Journal of Managed Care

Making PROgress with patient-reported outcomes

How PROs were successfully integrated into the Jakafi® (ruxolitinib) drug development program[1]

A novel approach to engage clinicians and FDA

PROs are an important means to demonstrate treatment benefits in clinical trials.[2,3] Use of a PRO instrument can evaluate symptoms best judged by the patient, whether caused by the disease or treatment toxicity. Assessment of symptom burden is important because it can be a major indicator of disease severity, progression or improvement. Incorporating PROs into a clinical trial program provides a means for evaluating the impact of therapy from the patient's perspective and helps patients and clinicians make better-informed decisions.[4]

TAILORING a PRO tool for myelofibrosis

Myelofibrosis (MF) is a life-threatening, progressive disease characterized by splenomegaly, debilitating symptoms and cytopenias.[5-7] Measures to assess both the splenomegaly and core symptoms of MF were incorporated into the phase III, double-blind placebo-controlled study, COMFORT-I, for Jakafi. Spleen reduction, as measured by imaging (MRI or CT), was the primary and biologic endpoint, and a reduction in total symptom score (TSS), the PRO measure, was a key secondary endpoint.[8,9] The TSS encompassed the following symptoms: abdominal discomfort, pain under left ribs, early satiety, pruritus, night sweats and bone/muscle pain.[9]

To include PROs in the trial, a novel instrument had to be specifically developed. After patient interviews, advice from clinical experts and extensive input from the FDA, the modified Myelofibrosis Symptom Assessment Form, version 2.0 (modified MFSAF v2.0) was finalized as part of the Special Protocol Assessment prior to the initiation of COMFORT-I. Ultimately, Jakafi was approved by the FDA for the treatment of intermediate or high-risk MF.[1,8] This became Incyte's first approved drug and also the first oncology medicine approved with symptom data in its label since the FDA's draft guidance on PROs was finalized in 2009.[2,4]

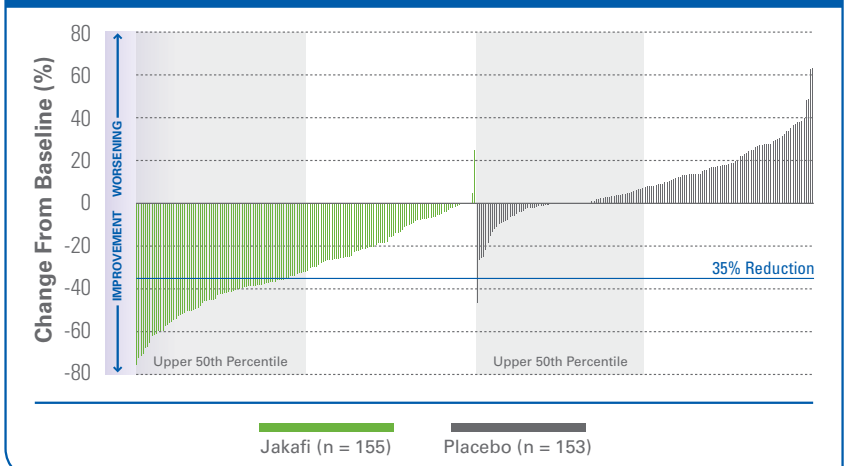
Indications and Usage
Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post–polycythemia vera myelofibrosis and post–essential thrombocythemia myelofibrosis.

Important Safety Information

- Treatment with Jakafi can cause hematologic adverse reactions, including thrombocytopenia, anemia and neutropenia, which are each dose-related effects, with the most frequent being thrombocytopenia and anemia. A complete blood count must be performed before initiating therapy with Jakafi. Complete blood counts should be monitored as clinically indicated and dosing adjusted as required
- The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache
- Patients with platelet counts <200 × 10^9/L at the start of therapy are more likely to develop thrombocytopenia during treatment. Thrombocytopenia was generally reversible and was usually managed by reducing the dose or temporarily withholding Jakafi. If clinically indicated, platelet transfusions may be administered
- Patients developing anemia may require blood transfusions. Dose modifications of Jakafi for patients developing anemia may also be considered
- Neutropenia (ANC <0.5 × 10^9/L) was generally reversible and was managed by temporarily withholding Jakafi
- Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral infections. Active serious infections should have resolved before starting Jakafi. Physicians should carefully observe patients receiving Jakafi for signs and symptoms of infection (including herpes zoster) and initiate appropriate treatment promptly
- A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or in patients with

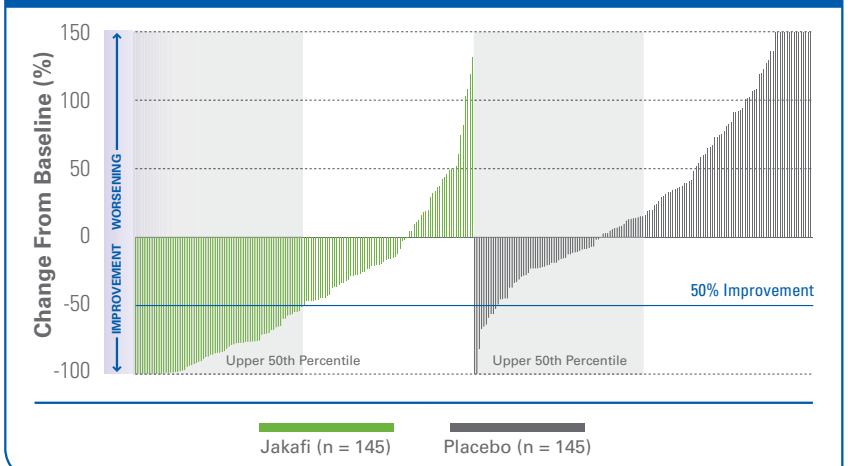
JAKAFI endpoints included both biologic and patient-reported outcomes[8,9]

COMFORT-I: Percent Change in Spleen Volume in Individual Patients From Baseline to Week 24 or Last Observation[9,a]



Each bar represents an individual patient's response.

COMFORT-I: Percent Change in TSS in Individual Patients From Baseline to Week 24 or Last Observation[9,a,b]



Each bar represents an individual patient's response. Worsening of TSS is truncated at 150%.

PROVIDING proof of patient benefit

MF is progressive, and spleen size and symptoms can become increasingly burdensome to patients over time.[5-7] Jakafi is proven to decrease total symptom score in patients with intermediate or high-risk MF—this is an important consideration when evaluating and treating patients.[9] The FDA approval included patients with intermediate-2 risk and high risk, as well as patients with intermediate-1 risk, since intermediate-1 patients may also have symptoms that require treatment. Clinical experience with Jakafi has shown that with the right process, manufacturers can successfully collaborate with regulatory agencies and academic experts to develop relevant and validated PRO instruments that can be incorporated into clinical trials.[1,8] The approval of Jakafi marks a significant milestone in which validated PRO instruments can provide symptom data and demonstrate clinical benefit. The experience with Jakafi may provide a model for the future use of PROs in marketing applications.[8]

renal or hepatic impairment *[see Dosage and Administration]*. Patients should be closely monitored and the dose titrated based on safety and efficacy

- There are no adequate and well-controlled studies of Jakafi in pregnant women. 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. Discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother

References: 1. McCallister E, et al. *BioCentury*. Reprint from December 5, 2011. **2.** Haley S. *The Pink Sheet*. November 21, 2011;73:47. Symptom Measurement in Clinical Trials. **3.** US Department of Health and Human Services Guidance for Industry: Patient-reported outcome measures: Use in medical product development to support labeling claims. December 2009. **4.** Basch E, et al. Issue brief from Conference on Clinical Cancer Research, November 2011. **5.** Cervantes F, et al. *Blood*. 2009;113:2895-2901. **6.** Mesa RA, et al. *Leuk Res*. 2009;33:1199-1203. **7.** Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807. **8.** Deisseroth AB, et al. *Clin Cancer Res*. 2012 Apr 27. (Epub ahead of print). **9.** Jakafi Prescribing Information. Incyte Corporation. November 2011. **10.** Data on File, Incyte Corporation.

[a] As studied in COMFORT-I, a randomized, double-blind, placebo-controlled phase III study with 309 total patients (United States, Canada, Australia). The primary endpoint was the proportion of subjects achieving a ≥35% reduction in spleen volume from baseline to Week 24 as measured by MRI or computed tomography (CT). A secondary endpoint was the proportion of subjects with a ≥50% reduction in TSS from baseline to Week 24 as measured by the daily patient diary, the modified MFSAF v2.0.[9,10]

[b] Symptom scores were captured by a daily patient diary recorded for 25 weeks. TSS encompasses debilitating symptoms of MF: abdominal discomfort, pain under left ribs, early satiety, 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.[9,10]

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

RUX-1130A 05/12

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 hematologic adverse reactions, including thrombocytopenia, anemia and neutropenia. A complete blood count must be performed before initiating therapy with Jakafi [*see Dosage and Administration (2.1) in Full Prescribing Information*]. Patients with platelet counts of less than 200 X 10^9/L at the start of therapy are more likely to develop thrombocytopenia during treatment. Thrombocytopenia was generally reversible and was usually managed by reducing the dose or temporarily withholding Jakafi. If clinically indicated, platelet transfusions may be administered [*see Dosage and Administration (2.2) in Full Prescribing Information*, *and Adverse Reactions*]. Patients developing anemia may require blood transfusions. Dose modifications of Jakafi for patients developing anemia may also be considered. Neutropenia (ANC less than 0.5 X 10^9/L) was generally reversible and was managed by temporarily withholding Jakafi [*see Adverse Reactions*]. Complete blood counts should be monitored as clinically indicated and dosing adjusted as required [*see Dosage and Administration (2.2) in Full Prescribing Information, and Adverse Reactions*]. **Infections** Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral infections. Active serious infections should have resolved before starting therapy with Jakafi. Physicians should carefully observe patients receiving Jakafi for signs and symptoms of infection and initiate appropriate treatment promptly. *Herpes Zoster* Physicians should inform patients about early signs and symptoms of herpes zoster and advise patients to seek treatment as early as possible [*see Adverse Reactions*].

ADVERSE REACTIONS 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 (2.6) 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 (2.4) 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 (2.5) 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 (2.5) in Full Prescribing Information*].

Incyte

Issued: November 2011 RUX-1040

Fluorescence in situ hybridization has been the "gold standard" for detecting ALK gene arrangement for some time, thanks in large part to it being the only companion diagnostic test approved by the US Food and Drug Administration for crizotinib treatment. However, in this issue of *Evidence-Based Oncology*, an article examines the efficacy of such a costly test (the author mentions that a 2011 *Forbes* article estimates the test to be ~$1500) and offers up an alternative testing option in the form of immunohistochemistry, another ALK testing method currently under evaluation.

The issue of cost is inseparable from healthcare, *especially* when it comes to oncology. In an era where targeted therapy is rapidly advancing, this issue is more relevant than ever. Companion diagnostics and pharmacogenomics are areas of medical science that have the potential to truly personalize care, especially in the oncology arena; however, the costs of many therapies and tests are highly problematic in that payers are not fully convinced that they are worth the investment and many patients are currently unable to afford them.

So, the obvious question becomes, where do we go from here?

Such a general, open-ended question might yield 100 different answers from 100 different healthcare professionals. One thought comes from C. Daniel Mullins, PhD, a healthcare economist at the University of Maryland School of Pharmacy and recent speaker at the Academy of Managed Care Pharmacy 24th Annual Meeting & Expo in San Francisco. Dr Mullins believes that, in order to better manage oncology costs, payers must achieve consensus from providers. Dr Mullins is not alone in this line of thinking. Barry Brooks, MD, medical oncologist with a community-based practice in Texas, expands on this thought by stating that providers would be more likely to buy into the importance of cancer pathways in lowering costs if payers would agree to 2 simple points. First, says Brooks, "Payers should agree to waive prior authorization requirements, which eat up considerable time and administrative resources and are perceived by physicians as a barrier to care." Secondly, they should "relinquish the right to retrospective reviews of care plans (outside of ensuring an evidence-based protocol is actually being used)." (Find out more about what Dr Brooks thinks at http://hcp.lv/ITZdWm).

The overall theory put forth by Drs Mullins and Brooks is that eliminating prior authorization can lead to higher quality. And, in the end, it's the pursuit of quality that is going to help revolutionize the entire healthcare system, not just as it pertains to oncology. It's quality that is going to unite all sectors of the healthcare industry. Quality is what is going to create buy-in from payers and providers so that, subsequently, patients will be able to afford timely care.

Thank you for reading.

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.

In This Issue...

THE AMERICAN JOURNAL OF MANAGED CARE

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

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

Chronic Myelogenous Leukemia

Jennifer Klemm, PhD; and Stanton R. Mehr

Chronic myelogenous leukemia (CML) is an acquired disorder in which the Philadelphia chromosome, a translocation between chromosomes 9 and 22, is acquired in hematopoietic stem cells, resulting in expression of the Bcr-Abl oncoprotein. Over 5000 Americans are diagnosed with CML each year.[1] Fortunately, the advent of tyrosine kinase inhibitor (TKI) therapy has dramatically extended life expectancy, with only 270 Americans expected to die of CML in 2011.[2] The introduction of TKI inhibitor therapy has effectively transformed CML into a chronic disease, and this contributes substantially to the economic burden associated with CML—the median survival of these patients exceeds 20 years.[3] A recent study demonstrated that medical costs for a patient with CML averaged $78,334 for just 1 year of treatment,[3] and TKI therapy must be given chronically or patients risk recurrence or progression to the advanced blast stage of CML, which can be life threatening.

Current Treatment Options

The primary front-line therapeutic option for CML is individual TKI treatment, specifically with imatinib, dasatinib, or nilotinib. Imatinib was the first TKI to be approved by the US Food and Drug Administration and is used primarily as first-line therapy—it is not approved for use after patients have tried dasatinib or nilotinib.[4] In contrast, both nilotinib and dasatinib were initially improved as second-line therapy after development of imatinib resistance.[5,6] However, recent trials have demonstrated that these agents may have advantages over imatinib as first-line therapy, particularly in patients with intermediate- or high-risk disease.[7-10] Longer-term follow-up of these studies is necessary to determine if these "second-generation" TKIs should become standard first-line therapy. For now, they are approved for newly diagnosed and imatinib-resistant disease only.[7,8]

Patients achieving a complete cytogenetic response with a first-line TKI remain on that therapy as long as their disease is in chronic phase. If patients do not achieve a complete cytogenetic response after 12 months of treatment with imatinib, they may receive higher-dose imatinib or switch to either nilotinib or dasatinib. For those receiving first-line nilotinib or dasatinib, treatment is often switched to the other second-generation TKI if their disease does not respond to initial therapy.

Some patients undergo mutational analysis of the Bcr-Abl kinase domain in order to choose the optimal second-line therapy, as both nilotinib and dasatinib are highly sensitive to specific mutations. In addition, mutational analysis can reveal the T315I mutation, which is resistant to all 3 TKIs; in patients with this mutation, allogeneic stem-cell transplantation is a reasonable option. Transplantation, which is the only curative treatment for CML, has lost favor as a first-line therapy with the advent of TKIs because of its high toxicity, including a 20% to 30% mortality rate,[9] its limited feasibility (due to donor availability), and high cost.[10]

If a patient receiving front-line TKI therapy achieves an insufficient response to treatment (less than complete hematologic response at 3 months, no cytogenetic response at 6 months, minor or no cytogenetic response at 12 months, or a partial cytogenetic response at 18 months) or if the disease reaches accelerated phase, treatment may be switched to a different TKI or an allogeneic transplant may be considered. Once a patient reaches blast crisis, options are generally restricted to a clinical trial or an allogeneic transplant preceded by a TKI with or without concurrent chemotherapy.[11,12]

Economics

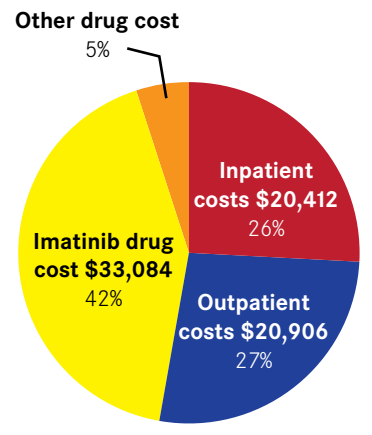
The management of CML is costly partially because patients continuously receive TKI therapy for many years. No clinical studies have yet shown that TKI therapy can be discontinued without patients experiencing relapse.

According to Medi-Span data as of December 2011, the wholesale acquisition cost per month of standard imatinib therapy is $5819, compared with $7882 for dasatinib and $8181 for nilotinib. The patent for imatinib expires in approximately 5 years, and a generic version could have a significant effect on pricing.

However, because some evidence suggests that nilotinib and dasatinib may have superior efficacy compared with imatinib in the front-line setting, these agents may be cost-effective in spite of their higher prices (in the present comparison). Further studies are needed to establish the cost-effectiveness of these second-generation agents relative to imatinib. Only retrospective health economic studies have examined the relative cost-effectiveness of nilotinib and dasatinib. For instance, a recent examination of claims from 521 patients with CML receiving second-line TKI therapy (452 receiving dasatinib, 69 receiving nilotinib) showed that patients taking dasatinib had nearly twice as many inpatient admissions (incidence rate ratio, 1.99; $P = .047$) and more than twice as many inpatient days (incidence rate ratio, 2.44; $P < .001$) compared with patients receiving nilotinib.[3] In addition, patients given dasatinib therapy had $8288 more medical service costs ($P < .001$), which were primarily associated with inpatient care. Finally, those taking dasatinib were found to be 13% less adherent to their medication than patients taking nilotinib ($P = .009$), despite the fact that nilotinib is taken twice daily and dasatinib is taken only once daily. Caution must be used when interpreting retrospective studies, but these data are intriguing. They are also consistent with another study of 267 patients, which demonstrated that patients with lower adherence to TKI therapy (in this case, imatinib) incurred higher annual medical costs.[13] In this study, patients with a medication possession ratio (MPR) of 75% incurred an additional $4072 in medical costs in 1 year compared with patients having an MPR of just 10% higher, or 85%.

An interesting issue involving these TKIs is that they are oral drugs rather than injectable oncology agents, and are covered sometimes as part of the medical

Figure. Annual Costs Associated With the Treatment of Chronic Myelogenous Leukemia



Reprinted with permission from Wu et al.[3]

Highlights From the 16th Annual International Congress on Hematologic Malignancies

PER PHYSICIANS' EDUCATION RESOURCE, LLC

Harry P. Erba, MD, PhD, associate professor, Department of Internal Medicine, University of Michigan Health System, discusses molecular monitoring for chronic myelogenous leukemia (http://hcp.lv/JvEY4l)

Harry P. Erba, MD, PhD, associate professor, Department of Internal Medicine, University of Michigan Health System, talks about monitoring a patient's response to chronic myelogenous leukemia therapy (http://hcp.lv/Je1aAN)

THE AMERICAN JOURNAL OF MANAGED CARE

Payer Perspective

Interview with Allan Jay Kogan, MD

***EBO*: In the majority of patients, chronic myelogenous leukemia (CML) is highly treatable with today's therapeutic agents. What has been the value of targeted treatment on value for the payer and the patient with CML?**

Dr Kogan: The introductions of the targeted tyrosine kinase inhibitors, such as imatinib, have made a great difference in terms of outcomes to patients with CML. As a health plan, we support the appropriate use of targeted treatment with biomarker testing.

***EBO*: Considering the state of the art in CML treatment today, what are your objectives in setting medical benefit policy to ensure optimal treatment?**

Dr Kogan: We use prior authorization to ensure that biomarker testing has been done, according to the prescribing information, before targeted treatment is undertaken.

***EBO*: What would you characterize as the determinants of good value in treating patients with CML today?**

Dr Kogan: We feel that the best value should be attained if we can achieve a remission with the fewest side effects. We would also prefer therapies with easy, convenient dosing to enhance compliance, especially since compliance seems to be a strong factor in averting recurrence. We also believe we can achieve greatest value if the regimen results in minimal interactions with other drugs the patient may be taking.

***EBO*: What are the key objectives as a payer when managing patients with CML?**

Dr Kogan: Obtaining a cure or remission with the fewest side effects would be the first objective. We want to avoid blast crisis, but it is difficult to determine who may be at higher risk for progression to blast crisis. It would be nice to have a biomarker to help in this respect. Stem-cell transplant is the most expensive treatment for CML. If we can avoid (not simply delay) the need for stem-cell transplant, that would create a very beneficial cost offset.

***EBO*: Does your plan contract with any major cancer treatment networks?**

Dr Kogan: Although we don't contract with major cancer networks, we do have preferred contracts with centers of excellence. The major benefits of these contracts are quality assurance and documentation of best outcomes. Most cancer networks want exclusive contracts, which would limit network negotiations with other needed providers geographically as a national health plan.

***EBO*: Does your health plan collaborate with any organizations to encourage members to participate in clinical trials in cancer treatment?**

Dr Kogan: No, we don't collaborate directly. Participation is determined by their employer's choice of benefit plan (if such participation is covered). This can vary by the level of trial (phase I, II, or III) and what exactly would be covered (everything related to usual care minus the experimental drugs and costs associated with monitoring/usage/administration of such drugs).

State regulations also influence this issue, as a number now require coverage for clinical trials for fully insured members (this does not apply to self-insured plans—which is why so many employers choose this approach, to avoid onerous, costly state mandates).

***EBO*: What types of investigational interventions hold the most promise for the future prevention/treatment of CML?**

Dr Kogan: That's a bit difficult to say, because CML is highly treatable in the chronic phase with today's therapeutic agents. I do think targeted, oral drug combinations with companion biomarker tests offer the best direction, with the best tolerance regarding side effects.

Dr Kogan is based in Dallas, Texas, and is the medical director for a national commercial health plan.

benefit versus the pharmacy benefit. In fact, since they are given on a continuing basis, many payers utilizing the pharmacy benefit elect to purchase and supply these agents through specialty pharmacy providers, who may have greater leverage with manufacturers (which results in somewhat lower prices).

Additional Drivers of the Cost of Care and Value

As expected, drug costs for patients with CML is the main driver of the cost of care, accounting for 42% of the total cost in one study examining costs incurred in the first year of care.[3] This is true not only because TKIs are expensive drugs, but also because they are given indefinitely, until patients reach advanced phase disease, which may take many years. For example, 55% of patients receiving imatinib as part of the pivotal IRIS trial were still taking the drug after 8 years.[14]

Aside from drug costs, both outpatient costs and inpatient costs are substantial as well, accounting for 27% and 26% of the total cost, respectively (**Figure**).[3] Examples of outpatient costs include both disease monitoring and mutational analysis. Although patients may receive TKI therapy and remain clinically stable for years, their response to therapy requires frequent monitoring. The National Comprehensive Cancer Network recommends that patients achieving a complete cytogenetic response to TKI therapy should receive Bcr-Abl transcript monitoring every 3 months for 3 years and every 3 to 6 months thereafter. The cost of this monitoring ranges from $375 to $1500 for each test.[15] However, since this type of monitoring is necessary to determine when therapy should be switched, this represents a necessary cost. Mutational analysis, which is often performed before choosing a specific TKI, is over $500.[16] Although this test is not absolutely necessary, it represents a good value for 2 reasons. First, it can provide a rationale for using imatinib over the more expensive second-generation TKIs if none of the mutations that are highly sensitive to either nilotinib or dasatinib are found. Second, if the patient is found to have the T315I mutation, no TKI therapy should be used, since that mutation is associated with poor response to all current TKI therapeutic agents.

***Funding Source*:** None.

***Author Disclosures*:** Mr Mehr reports receiving payment for involvement in the preparation of this article. Dr Klemm reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

***Authorship Information*:** Concept and design (JK); acquisition of data (SRM); analysis and interpretation of data (SRM); drafting of the manuscript (JK, SRM); and critical revision of the manuscript for important intellectual content (JK, SRM). **EBO**

References

1. American Cancer Society. Cancer Facts & Figures 2011. Atlanta: American Cancer Society; 2011.

2. Quintas-Cardama A, Cortes JE. Chronic myeloid leukemia: diagnosis and treatment. *Mayo Clin Proc*. 2006;81:973-988.

3. Wu EQ, Guerin A, Yu AP, Bollu VK, Guo A, Griffin JD. Retrospective real-world comparison of medical visits, costs, and adherence between nilotinib and dasatinib in chronic myeloid leukemia. *Curr Med Res Opin*. 2010;26:2861-2869.

4. Gleevec [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2011.

5. Sprycel [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2011.

6. Tasigna [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2011.

7. Kantarjian H, Shah NP, Hochhaus A, et al.

"The best value should be attained if we can achieve a remission with the fewest side effects."

—Allan Jay Kogan, MD
Medical Director

Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2010;362:2260-2270.

8. Kantarjian HM, Shah NP, Cortes JE, et al. Dasatinib or imatinib in newly diagnosed chronic phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION) [published online ahead of print December 9, 2011]. *Blood*.

9. Kantarjian HM, Hochhaus A, Saglio G, et al. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. *Lancet Oncol*. 2011;12:841-851.

10. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362:2251-2259.

11. Hehlmann R, Pfirrmann M, Hochhaus A, et al. Randomized comparison of primary allogeneic stem cell transplantation and best available drug treatment in chronic myeloid leukemia (abstract). *Blood*. 2006;108:Abstract 427.

12. NCCN Clinical Practice Guidelines in Oncology. Chronic Myelogenous Leukemia. V2.2012. National Comprehensive Cancer Network website. http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Accessed January 2, 2012.

13. Darkow T, Henk HJ, Thomas SK, et al. Treatment interruptions and non-adherence with imatinib and associated healthcare costs: a retrospective analysis among managed care patients with chronic myelogenous leukaemia. *Pharmacoeconomics*. 2007;25:481-496.

14. Deininger M, O'Brien SG, Guilhot F, et al. International randomized study of interferon vs STI571 (IRIS) 8-year follow up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib (abstract). *Blood*. 2009;114:Abstract 1126.

15. Sessions J. Chronic myeloid leukemia in 2007. *J Manag Care Pharm*. 2007;13(8)(suppl A):4-7.

16. BCR/ABL, p190, mRNA detection, reverse transcription-PCR (RT-PCR), quantitative, monitoring assay. Mayo Medical Laboratories. http://www.mayomedicallaboratories.com/test-info/hematology/catalog/Fees+and+Coding/83336. Accessed January 2, 2012.

Additional Suggested Reading

Hoyle M, Rogers G, Moxham T, Liu Z, Stein K. Cost-effectiveness of dasatinib and nilotinib for imatinib-resistant or -intolerant chronic phase chronic myeloid leukemia. *Value Health*. 2011;14:1057-1067.
A UK National Health Service perspective on the cost-effectiveness of dasatinib and nilotinib compared with high-dose imatinib for patients with chronic-phase CML who are resistant to normal-dose imatinib and compared with interferon-α for people intolerant of imatinib.

Ghatnekar O, Hjalte F, Taylor M. Cost-effectiveness of dasatinib versus high-dose imatinib in patients with chronic myeloid leukemia (CML), resistant to standard dose imatinib—a Swedish model application. *Acta Oncol*. 2010;49:851-858.
Swedish researchers assess the cost-effectiveness of dasatinib versus high-dose imatinib treatment in chronic phase CML patients who are resistant to lower doses of imatinib.

Reed SD, Anstrom KJ, Li Y, Schulman KA. Updated estimates of survival and cost effectiveness for imatinib versus interferon-alpha plus low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukaemia. *Pharmacoeconomics*. 2008;26:435-446.
Researchers from Duke University evaluated survival data from the IRIS (International Randomized study of Interferon vs STI571) trial to update cost-effectiveness estimates, based on 19 months of follow-up, of imatinib versus interferon-α plus low-dose cytarabine in patients with chronic-phase chronic myeloid leukemia. When applying medication costs, incremental cost-effectiveness ratios were between $42,000 and $57,500 per quality-adjusted life-year.

Breitscheidel L. Cost utility of allogeneic stem cell transplantation with matched unrelated donor versus treatment with imatinib for adult patients with newly diagnosed chronic myeloid leukaemia. *J Med Econ*. 2008;11:571-584.
A study of cost-effectiveness from the perspective of the German statutory health insurance evaluated the cost utility of allogeneic stem cell transplantation relative to imatinib in patients newly diagnosed with chronic-phase chronic myeloid leukemia.

Szabo SM, Levy AR, Davis C, Holyoake TL, Cortes J. A multinational study of health state preference values associated with chronic myelogenous leukemia. *Value Health*. 2010;13:103-111.
In this study, Canadian researchers evaluated preferences in patients from 4 developed countries, correlating CML disease progress with deteriorating health preference scores.

Ramchandren R, Schiffer CA. Dasatinib in the treatment of imatinib refractory chronic myeloid leukemia. *Biologics*. 2009;3:205-214.
The second-generation TKI dasatinib demonstrated efficacy in several studies of patients whose CML has progressed. This paper reviews the current clinical trial data on dasatinib.

Hochhaus A, O'Brien SG, Guilhot F, et al. Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. *Leukemia*. 2009;23:1054-1061.
An extended follow-up was conducted of patients enrolled in the landmark International Randomized Study of Interferon vs STI571 (IRIS) investigation of the effectiveness of imatinib in CML. The estimated event-free survival at 6 years was 83%, and the estimated rate of freedom from progression to acute phase and blast crisis was 93%, with an estimated overall survival of 88% (95% when only CML-related deaths were considered).

General information on chronic myelogenous leukemia. National Cancer Institute. http://www.cancer.gov/cancertopics/pdq/treatment/CML/HealthProfessional.
Information for the health professional on the etiology, incidence and mortality, and treatment of CML.

Parker WT, Ho M, Scott HS, Hughes TP, Branford S. Poor response to second-line kinase inhibitors in CML patients with multiple low-level mutations, irrespective of their resistance profile [published online ahead of print December 30, 2011]. *Blood*.
Although specific imatinib-resistant Bcr-Abl1 mutations (Y253H, E255K/V, T315I, F317L, F359V/C) predict failure of second-line nilotinib and/or dasatinib therapy in patients with CML, 40% of patients with chronic phase disease but without these resistant mutations also fail. Australian researchers investigated whether sensitive mutation analysis could identify other poor-risk subgroups.

Tantiworawit A, Power MM, Barnett MJ, et al. Long-term follow-up of patients with chronic myeloid leukemia in chronic phase developing sudden blast phase on imatinib therapy [published online ahead of print December 22, 2011]. *Leuk Lymphoma*.
Sudden blast phase is a rare event that occurs unpredictably in patients with CML who otherwise appear to be responding to imatinib treatment. The authors characterized 9 of 213 patients with chronic phase CML treated with imatinib who developed sudden blast phase.

Baghdadi TA, Abonour R, Boswell HS. Novel combination treatments targeting chronic myeloid leukemia stem cells [published online ahead of print December 15, 2011]. *Clin Lymphoma Myeloma Leuk*.
Although Bcr-Abl inhibitors eradicate most CML cells, they are largely ineffective against the reservoir of quiescent leukemic stem cells (LSCs). Thus, a strong medical need exists for therapies that effectively eradicate LSCs and is currently a focus of extensive research. The authors outline new approaches to addressing LSC eradication.

THE AMERICAN JOURNAL OF MANAGED CARE

Provenge Angst
(continued from Cover)

Those hopes were challenged as Dendreon announced a slowing of sales versus estimates for the later quarters of 2011. This article will explore some of the issues behind the launch of Provenge, and discuss, from a community oncology perspective, whether the Provenge story reflects a rapidly changing landscape that moved faster than was anticipated for a new drug launch or rather serves as a claxon warning for revision of expectations for new drugs related to oncology for the future.

Typical Launch Delays in Production and Approval. Provenge, an autologous cell therapy, first won US Food and Drug Administration (FDA) approval in April 2010, and was officially launched the following month. CMS resolved national uncertainty over whether it would reimburse for Provenge at the end of March 2011, and after much national attention was drawn by the cost of the treatment ($93,000 for 3 infusions of the vaccine over 30-40 days), CMS announced that it would reimburse for Provenge when used for its approved indication. Private insurers continued to watch both the efficacy and the cost of the new treatment, and put into place a combination of prior authorization and post-claim medical reviews for physicians wishing to prescribe the treatment for their patients.[1]

tended its sales force activities out into the community, targeting both oncology and urology practices. Those sites now number over 800, yet the investment community is still wondering if final 2012 sales will reach expectations.[2]

Atypical Questioning of Launch and Sales. More questions have surrounded the launch of Provenge than any other oncology product in recent history. This launch is unique for a few reasons. It is a novel treatment, using the patient's own cells to create the product. There is not likely to be a generic version of this treatment on the horizon. The patients do not have many other options—this is for a specific group of end-stage prostate cancer patients. Ultimately, survival is not an end product of this treatment, but it does seek to extend life for patients by a margin without complications of chemotherapy alternatives. Potential patients are found primarily in the community practices of both urologists and oncologists.

Questions from market analysts regarding the Provenge launch have centered around issues such as price, potential lack of patient demand, potential lack of education of physicians regarding access and administration, and particularly the probability and speed of reimbursement. None of these are new issues, and particularly not for oncology drugs. What happened during this product launch to cause such angst for Provenge?

Competition Rising Quickly
Approval for Zytiga on the Horizon?

In the fall of 2011, while Provenge was still making news as a front-runner treatment for prostate cancer, another treatment, this time taken as a twice daily oral pill, was being approved for a slightly different indication.[1] Zytiga, made by Johnson & Johnson, was first approved in 2011 for men with prostate cancer who had previously failed chemotherapy. However, a recent clinical trial was halted early by independent data monitors due to findings which, if approved, would move Zytiga into direct competition with Provenge for men with less advanced prostate cancer.[2]

The nature of cancer research and treatment is that the unexpected is likely to prevail. With hundreds of clinical studies under development, new information is produced each year in peer-reviewed journals and clinical meetings, and submitted for approval. Placement of a new drug on the market requires a delicate balance of pricing strategy, proven efficacy under parameters whose importance sometimes varies with the beholder, and some degree of luck in terms of uptake on the part of patients, physicians, and health plans. If drugs are then held up in scrutiny to alternatives and found to have comparative issues on any of a number of fronts, it could be a challenge to its market success and position, no matter how new the drug itself is. There are differences in delivery, perceived convenience, and medical efficacy between Zytiga and Provenge that are now very much a part of the clinical discussion and ultimately will play out in the market.

References

1. Pierson R. Zytiga creeps up on Provenge prostate-cancer drug. Reuters.com website. http://www.reuters.com/article/2011/10/07/us-dendreon-zytiga-idUSTRE7965JF20111007. Published October 27, 2011. Accessed April 27, 2012.

2. Feuerstein A. J&J prostate cancer drug scores big win, hurts Dendreon, helps Medivation. Thestreet.com website. http://www.thestreet.com/_yahoo/story/11448569/1/jj-prostate-cancer-drug-scores-big-win-hurts-dendreon-helps-medivation.html?cm_ven=YAHOO&cm_cat=FREE&cm_ite=NA <http://www.thestreet.com/_yahoo/story/11448569/1/jj-prostate-cancer-drug-scores-big-win-hurts-dendreon-helps-medivation.html?cm_ven=YAHOO&cm_cat=FREE&cm_ite=NA> . Published March 8, 2012. Accessed April 27, 2012.

> *"No longer was simple approval by the FDA a blanket pass into uptake in the medical community."*
>
> **—Dawn G. Holcombe, MBA, FAMCPE, ACHE**
> President, DGH Consulting

Capacity issues constrained the initial drug launch for much of the first 12 months it was on the market. Full-scale production wasn't achieved until May 2011, which limited the number of sites at which the drug could be launched. Initial focus of distribution of Provenge was limited mostly to about 50 academic hospitals and cancer centers, despite more than two-thirds of asymptomatic or minimally symptomatic metastatic, castration-resistant prostate cancer (CRPC) patients being treated in community practice settings.[1] After the production issues were resolved, Dendreon ex-

Timing Is Everything: Provenge Entered the Market During Tumultuous Times

Recent Reimbursement Changes. Since 2003, when the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) was passed, drug reimbursements for oncology have steadily declined. Medicare now pays based upon a market calculation of cost that doesn't match the direct and indirect expenses that physicians incur to buy drugs for treatment. This Average Sales Price (ASP)-based reimbursement rate was adopted by Medicare in 2005 and more slowly by private insurers. By 2010, a cancer center (private or hospital-based) could see from 50% to 75% or more of its drugs reimbursed on an ASP basis. After factoring in both direct and indirect costs of drug acquisition, stocking, and handling, many practices could hope, at best, for breakeven on most of the drugs they stock. However, at the same time, private payers were rapidly ramping up oncology drug management processes, such as prior authorizations and reviews of medical necessity.

Increasing Pressures for Costly Technology. Medical providers, both hospitals and physician practices, have faced rapidly escalating demands for information technology, including electronic medical records that can track and report on certain measures. The American Recovery and Reinvestment Act of 2009 (ARRA) was signed into law on February 17, 2009. The ARRA was intended to kick-start healthcare investments in information technology, and in so doing, it created significant financial pressures on healthcare providers, which had already tight operating margins to fund technology initiatives.

Increased Patient Financial Responsibility. Following the passage of the MMA in 2003, new Medicare Advantage Plans and private insurers started pushing greater financial responsibility for care upon the patients. Rising costs of care, driven by combination drug regimens and higher drug prices, even affected Medicare patients with regular Medicare insurance. If those regular Medicare patients did not also have supplemental insurance to assist with the 20% for which they are responsible, treatments could become unmanageable for those patients.

Community Practices and Provenge

As operational margins tightened for medical practices, cash flow assumed great importance. Practices could often see delays in payment due to medical reviews and other payer processes of 30, 60, or even 90 days. In earlier years, margins on practice operations could more easily cover those cash flow delays, but by 2010, practices were feeling such financial pressure that timing of cash flow and cash outlays became very important, even if a drug were to be ultimately covered and funded. According to an Updated Practice Closings Report released by the Community Oncology Alliance in March 2011, more than 1000 cancer clinics nationwide have experienced closings or financial struggles to pay bills, have sent patients elsewhere for treatment, or have been acquired by other entities. Dr David Eagle, president of the Community Oncology Alliance, reports that these closings are due to both Medicare reimbursement cuts since 2004 and increasing numbers of private insurers following the Medicare pattern of reimbursement cuts.[3]

With increasing health plan focus on appropriate use and prior authorizations came a large stick: If a treatment did not get appropriate prior authorization, or was found under subsequent medical review not to be covered, it was the practice that tended to absorb the loss.

It would not be uncommon by 2010 and 2011 for a practice or physician to look at a newly approved drug, try it

initially for 1 patient, and observe not only the financial approval and reimbursement patterns for that drug, but also compare the results of the drug for their own patient against the published trial results. New drugs were being exposed to a much higher level of scrutiny in the real world medical community than ever before. No longer was simple approval by the FDA a blanket pass into uptake in the medical community.

"Cash flow for oncology care and operational concerns have now become a permanent fixture in the treatment of cancer for the providers, the health plans, and the patients."

—Dawn G. Holcombe, MBA, FAMCPE, ACHE
President, DGH Consulting

Current Physician Community Perspectives on Provenge

For this article, local practices in Connecticut were interviewed on their current experiences and concerns regarding Provenge. While concerns about whether or not the treatment will be covered seem to have lessened, cash flow for payment, financial impact on the patient for copays and co-insurance (even for Medicare patients), and performance efficacy of the treatment in light of the cost of treatment continue to be significant themes.

Indications and Appropriateness. One oncology physician noted that they continue to see occasional problems with Provenge, primarily because of detailed oversight and insurance expectation that treatment will follow FDA approval very closely. Another practice administrator indicated that although they are one of the busiest practices in the area, they have not yet put any patients on Provenge, stating however that they believe one patient will soon meet the criteria. Conversely, it was noted that so much goes into pre-authorization before the patient is put into the process that the practice feels well assured of payment before the process begins.

Cash Flow. It appears from the responding practices that cash flow is still a concern, but the depth of the concern may vary depending on the practice and the respondent. One practice administrator noted that drug distributor delays of drug payment due date of up to 90 days is very helpful. However, she went on to note that if a practice has more than 1 patient on Provenge, it needs to plan carefully for making that payment when the 90 days is up. If the practice has more than 1 patient on at a time, a due bill of over $100,000 could be significant for any practice. That administrator also wondered whether the payment terms for product could be restricted now that the Q code has been issued. Another physician noted that patient acceptance has been generally poor (from a financial rather than clinical standpoint). Another practice administrator noted that with practices across the country experiencing significant cash flow problems related to the Medicare implementation of new software (5010), any high dollar amount item for any reason is being closely scrutinized.

Patient Impact. Concern was still expressed over the financial impact on the patient. Dendreon was complimented for the resources that it does make available to patients, but there were concerns over not only the impact on the patients who do not qualify for needed assistance, but also the burden on the patients and practice of the process for obtaining assistance. Even if assistance is found, the burden on human capital in the administrative and education process is significant, and may be untenable for a private practice or for the patient relative to the medical opportunity afforded by the treatment. A 2010 survey by the Association of Oncology Social Work reported that as many as 68% of cancer patients and caregivers reported that the patient is experiencing financial hardship due to medical bills. The survey also reported that about 49% had stopped treatments, skipped medications, or missed doctor's appointments due to the financial burden, and many more never start treatment at all because of the catastrophic costs of cancer care.[4]

Value. Value, like anything, is found in the eye of the beholder. Both patients and physicians still express concern over the balance between the efficacy and benefit of the treatment versus the cost of obtaining that treatment. Even when patients have insurance that pays the bulk of the expense, cost is still considered as part of their evaluation process. The physicians who were interviewed, while not a significant sample, were interesting in that they all expressed either their own or their patients' concern with the clinical experience in comparison with the literature or when compared with alternatives.

Conclusion: Both a Symbol and Victim of the Times

As will be done with many more oncology treatments to come, Dendreon pushed to develop an individualized treatment for a patient population with few other alternatives. Under other circumstances, this innovation would have been lauded more than questioned. But, because of the maelstrom of financial pressures hitting practices, patients, and health plans alike, what was probably planned to be a conventional launch was beset with questions about value, pricing, efficacy, and slow uptake in its primary market, the community practice.

The new reality for any drug launch is now probably a litany of what Dendreon experienced:

- Increasing scrutiny of efficacy against alternatives (**Sidebar**; but probably with an expectation that such efficacy will be measured in half, three-quarter, or full years rather than a few months).
- FDA approval may mean acceptance on Medicare formularies, but health plans may accept FDA approval or conduct their own reviews for what they consider to be medical appropriateness. Physicians may increasingly slowly adopt a product under FDA approval within their own practice, but observe treated patients for actual clinical experience in comparison with the published literature—as much for their own clinical satisfaction as for their ability to explain medical necessity to a health plan when prescribing the product.
- Patients may consider treatment options, even if FDA approved, and decide to proceed or not based upon their own financial benefit package and personal situation. Dollars paid are being weighed heavily as debt incurred for a family that will linger once the patient is gone.
- Cost of product acquisition and timing of payment of that debt related to payment for treatment using that product are increasingly important to physician practices. Cash flow will be measured, and the higher-priced products may be subject to volume limitations on numbers of patients being treated at the same time to reduce exposure, and in the process, restrict market volume.

These concerns will remain whether treatment is delivered in a physician office or a hospital setting. Cash flow for oncology care and operational concerns have now become a permanent fixture in the treatment of cancer for the providers, the health plans, and the patients. Value is a function of all these pressures on the involved entities, as well as on the pharmaceutical company that develops the innovative treatment. For good or bad, that value equation has changed forever, and will actually continue to evolve as we learn more about the actual performance of all the alternatives for oncology treatment in the clinical setting. This may be a surprise message for financial market investors, but the physicians, patients, and health plans have been living with this reality for several years. Good products with strong efficacy will launch and do well, even if it is more slowly than expected based upon old market rules. **EBO**

***Author Affiliation*:** From DGH Consulting, South Windsor, CT.

***Funding Source*:** None.

***Author Disclosure*:** The author reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

***Authorship Information*:** Concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

References

1. Shaeffer S. Dendreon's curve ball. BioCentury website. http://www.biocentury.com/biotech-pharma-news/coverstory/2011-08-08/why-dendreon-stumbled-on-its-launch-of-provenge-for-prostate-cancer-a1. Published August 8, 2011.

2. Cohen T. Dendreon: where do things stand on Provenge reimbursement? Seekingalpha .com website. http://seekingalpha.com/article/315329-dendreon-where-do-things-stand-on-provenge-reimbursement. Published December 21, 2011. Accessed February 29, 2012.

3. Pace of community cancer clinics closures increasing: an escalating trend [press release]. Washington, DC: Community Oncology Alliance, redOrbit.com, PRNewswire; March 31, 2011. http://www.redorbit.com/news/health/2022226/pace_of_community_cancer_clinic_closures_increasing_an_escalating_trend/. Accessed February 29, 2012.

4. Mellace J. The financial burden of cancer care. Social Work Today website. http://www.socialworktoday.com/archive/032210p14.shtml. Published March/April 2010. Accessed February 28, 2012.

Testing for ALK-Positive NSCLC

Signaling the Future of Personalized Medicine

Keith Beagin

Recent studies offer new insights into ALK detection methods and related treatments. Screening for the non-small cell lung cancer (NSCLC) subtype has been at the forefront of NSCLC research, and numerous published studies have established meaningful results spanning a vast spectrum of testing approaches. While fluorescence in situ hybridization (FISH) has been the "gold standard" of detecting ALK gene rearrangement, several clinical trials evince limitations in this method—in terms of both cost and effectiveness—and oncologists and other medical professionals suggest administering a combination of screening methods to adequately identify ALK-positive NSCLC. The US Food and Drug Administration (FDA) has recently approved FISH as the sole testing method for ALK gene rearrangement. Further, it is also the prescreening step for ALK treatment eligibility. Crizotinib (Xalkori), an orally taken ALK inhibitor, is currently the only FDA-approved drug treatment for ALK non-small cell lung cancer, and since its prescription is entirely contingent upon positive FISH results, many researchers promote the standardization of other screening methods, which could be more accurate and cost efficient. Many payers, however, argue that the efficacy of FISH is enough to validate its usage, and that this current trend of companion diagnostic devices will, in the long run, promote more efficient use of treatment and better patient outcomes.

Anaplastic Lymphoma Kinase

Anaplastic lymphoma kinase, or ALK, is a subset of non-small lung cancer that represents about 4% of lung adenocarcinomas.[1] This subset was discovered in a 2007 Japanese study that identified "a fusion gene comprising portions of the echinoderm microtubule-associated protein-like (EML4) gene and the anaplastic lymphoma kinase (ALK) gene…."[2] Interestingly, ALK rearrangement is almost exclusively found in non-smokers, or light smokers (less than 10 packs a year). Further, researchers have identified at least 13 known variants of the EML4-ALK fusion gene, a characteristic often cited as diagnostically problematic, especially given the rareness of ALK rearrangement.

In August 2011, the FDA approved the oral ALK inhibitor crizotinib (licensed by Pfizer under the brand name Xalkori), and it is currently considered the standard method of treatment for ALK-positive NSCLC. Prescription, though, is contingent upon the testing for and subsequent positive identification of ALK rearrangement. To meet this requirement, the FDA approved Abbott Laboratories' Vysis Break Apart FISH Probe Kit as the sole companion test to crizotinib treatment. This test-treatment combination is part of the larger trend of personalized medicine development, and it represents what Jenifer Antonacci, director of media relations, Pfizer Inc, calls "a shift away from a one-size-fits-all approach, toward biomarker-based treatment decisions." But with FISH's high up-front costs and wavering results, many still question the viability of offering the FISH kit as the sole screening method for NSCLC patients.

Testing for and Treatment of ALK-Positive Non-Small Cell Lung Cancer

FISH continues its reputation as the "gold standard" for ALK screening. Being the only FDA-approved companion diagnostic test to crizotinib treatment, its diagnostic merit and cost are sources of much controversy among medical professionals. The test's diagnostic challenges are often cited in the literature. For instance, a 2011 multi-institutional study by Paik et al reported that out of 735 NSCLC patients, FISH identified ALK-gene rearrangement in only 28 patients (3.8%), while immunohistochemistry (another ALK testing method currently under evaluation) identified 55 patients (7.5%) as ALK positive.[3]

More important, FISH is an expensive procedure, its steep cost further compounded by laboratory fees. A 2011 *Forbes* article prices a FISH test at ~$1500, which includes the cost of the test (~$250) and pathology services.[4] Further, because Abbott's FISH kit is biomarker-based (the Vysis FISH kit is optimized to locate *only* ALK gene mutations), it supposes a potential waste of resources; the same *Forbes* article finds that only 1 out of 25 ALK-tested patients actually test positive for ALK gene rearrangement. As a result, oncologists and subspecialists are working to standardize a more diagnostically effective and economical method for ALK screening. When asked about the economic implications of FISH, Joanne E. Yi, MD, anatomic pathology and clinical pathology, Mayo Clinic, had this to offer: "Most community pathology laboratories do not have the equipment or personnel to perform this test, and they usually send out to reference laboratories. FISH probe for ALK translocation in a lung cancer setting is now more expensive since the FDA approved the drug with the (FISH) companion test…the prevalence of ALK translocation is so low, and if you do cost analysis it (alternative testing and treatment) will be still much cheaper even if you reflex to more FISH."

Nonetheless, proponents of FISH cite the method's newly improved assays and ability to positively identify ALK translocation without further validation by other diagnostics as acceptable reasons for its standardization.[1] Many also propose administering a combination of screening methods should FISH produce a false negative.

Health plan professionals, as well, are championing the apparent success of companion diagnostic devices like FISH. They argue that the potential effectiveness of a biomarker-based test like FISH outweighs its high cost, and that as a prescreening step before treatment, it enables payers and patients to avoid much higher expenditures on what would be unnecessary treatment.

Crizotinib (Xalkori) was approved by the FDA in August 2011, and is targeted therapy for the treatment of ALK-positive NSCLC. Responses to the drug have been mostly favorable, with the results of the initial drug trials showing a 57% response rate after just 8 weeks of treatment.[5] While adverse effects have been reported, all are relatively mild, with the most severe being temporary visual impairment (Table).[6]

Much like its companion FISH test, however, crizotinib comes with a high cost. In 2011, Emaxhealth.com reported that crizotinib costs approximately $9600 a month, and with its reliance

Table. Most Common Treatment-Related Adverse Events (≥10%) With Crizotinib (N = 113)[a]

Adverse event	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Total, n (%)
Nausea	58 (51.3)	1 (0.9)	0	0	59 (52.2)
Diarrhea	55 (48.7)	2 (1.8)	0	0	57 (50.4)
Visual impairment	51 (45.1)	0	0	0	51 (45.1)
Vomiting	46 (40.7)	1 (0.9)	0	0	47 (41.6)
Constipation	22 (19.5)	6 (5.3)	0	0	28 (24.8)
Peripheral edema	19 (16.8)	3 (2.7)	0	0	22 (19.5)
Decreased appetite	21 (18.6)	0	0	0	21 (18.6)
Dizziness	21 (18.6)	0	0	0	21 (18.6)
Fatigue	14 (12.4)	3 (2.7)	1 (0.9)	0	18 (15.9)
Alanine aminotransferase increased	3 (2.7)	6 (5.3)	4 (3.5)	1 (0.9)	14 (12.4)

[a]Reprinted with permission from Camidge et al.[6]

Payer Perspective

Will the current trend of personalized medicine ultimately engender a future of improved healthcare? In a recent interview, **Robert McDonough, MD**, Clinical Policy Research & Development, Aetna, discussed the impact of ALK testing and other companion diagnostics on policy making and patient outcomes:

***EBO*: Does Aetna currently cover the costs of both FISH testing and crizotinib treatment?**
Dr McDonough: This is an interesting treatment, because you have an oral medication that's covered under your pharmacy benefits, and then you have a companion diagnostic that would be covered under medical benefits. Yes, we would cover both for their approved indications at this time.

***EBO*: Do you see other health plans jumping on board with offering both of these recently FDA-approved components?**
Dr McDonough: I think that you're going to see pretty uniform coverage for the test and the treatment. It is an FDA-approved treatment for cancer. I believe the National Comprehensive Cancer Network has (also) endorsed the use of this for the treatment of people with NSCLC.... To ensure that the product is working appropriately, you would cover, under the medical benefits, the FISH test that's used.

***EBO*: To what extent does the cost of FISH factor into your coverage decisions?**
Dr McDonough: This is an important point–we make the coverage decision based on the evidence of effectiveness. The cost-effectiveness is factored into the coverage decision only after you've made the coverage decision.... Aetna has agreed to cover cancer drugs with indications that are recognized by the NCCN of level II/B or greater. So in addition to FDA approvals, the NCCN guidelines are factored into our coverage decision.

***EBO*: So with research indicating that only 1 out of 20 or 25 patients will actually test positive for ALK gene rearrangement, do you find covering the costs of FISH is in any way a waste of resources? Is it problematic?**
Dr McDonough: The nice part about this (FISH) test is that it allows you to focus on the 1 out of 20 patients that would actually benefit from this (Xalkori) drug. It actually allows for more efficient use of resources. Also, the drug has adverse effects, some that are potentially serious. So in using this test, you're able to focus the use of the drug on the people that benefit, and not expose the 19 out of 20 patients who will not benefit, from the risks, including the adverse reactions, by exposure to this drug.

***EBO*: Pfizer is currently offering the Xalkori drug in conjunction with a $100 copay assistance program for underinsured patients whose health plans do not offer coverage. Do you think it is in these patients' best interest to pay out of pocket for the FISH test?**
Dr McDonough: Yes. It (the cost of FISH) is minimal to the cost of the drug. You would want to know if you're 1 out of 20.

***EBO*: A stipulation of that Pfizer program is that it only allows a maximum annual savings of $24,000, which is approximately 2 months' worth of treatment. Isn't this an inadequate amount of treatment for the average ALK-positive patient? What does the underinsured patient do in this scenario?**
Dr McDonough: Yes. The average patient is on the drug for about 10 to 11 months...But I imagine that the program is allowing coverage with the idea that in the meantime, the patient will be getting coverage, or getting on Medicaid, or some other arrangement where they will get coverage for continued treatment.

***EBO*: Both Abbott's FISH kit and Pfizer's Xalkori represent a recent breakthrough in personalized cancer treatment. Do you foresee an emergence of potential competitors?**
Dr McDonough: Not so much competitors. What I see is that this is a trend. The idea of having tests that determine whether someone should be eligible for certain treatments...I think in the future we're going to see many more examples of drugs that are developed in tandem with diagnostic tests, or also the development of diagnostic tests after drugs come out. I think you will see both. The idea is that you can focus treatment on the subgroup of patients who would benefit the most.

***EBO*: So, to conclude, you view this trend of personalized medicine as beneficial to patient outcomes overall?**
Dr McDonough: I think it will benefit patient outcomes, and also lead to a more efficient use of resources...The development of these companion diagnostics is essential to be able to demonstrate the benefits of a specific therapy, especially a specific therapy that only benefits a small subgroup of patients with a particular condition. So I do think we're going to see more development of these companion diagnostic devices. In fact, the FDA has offered some direct guidance for industry on the development of these companion diagnostics, so it's definitely going to be a trend in the future.

on the FISH probe kit as a companion test, the total cost of ALK screening and treatment would be "prohibitive for many."[7]

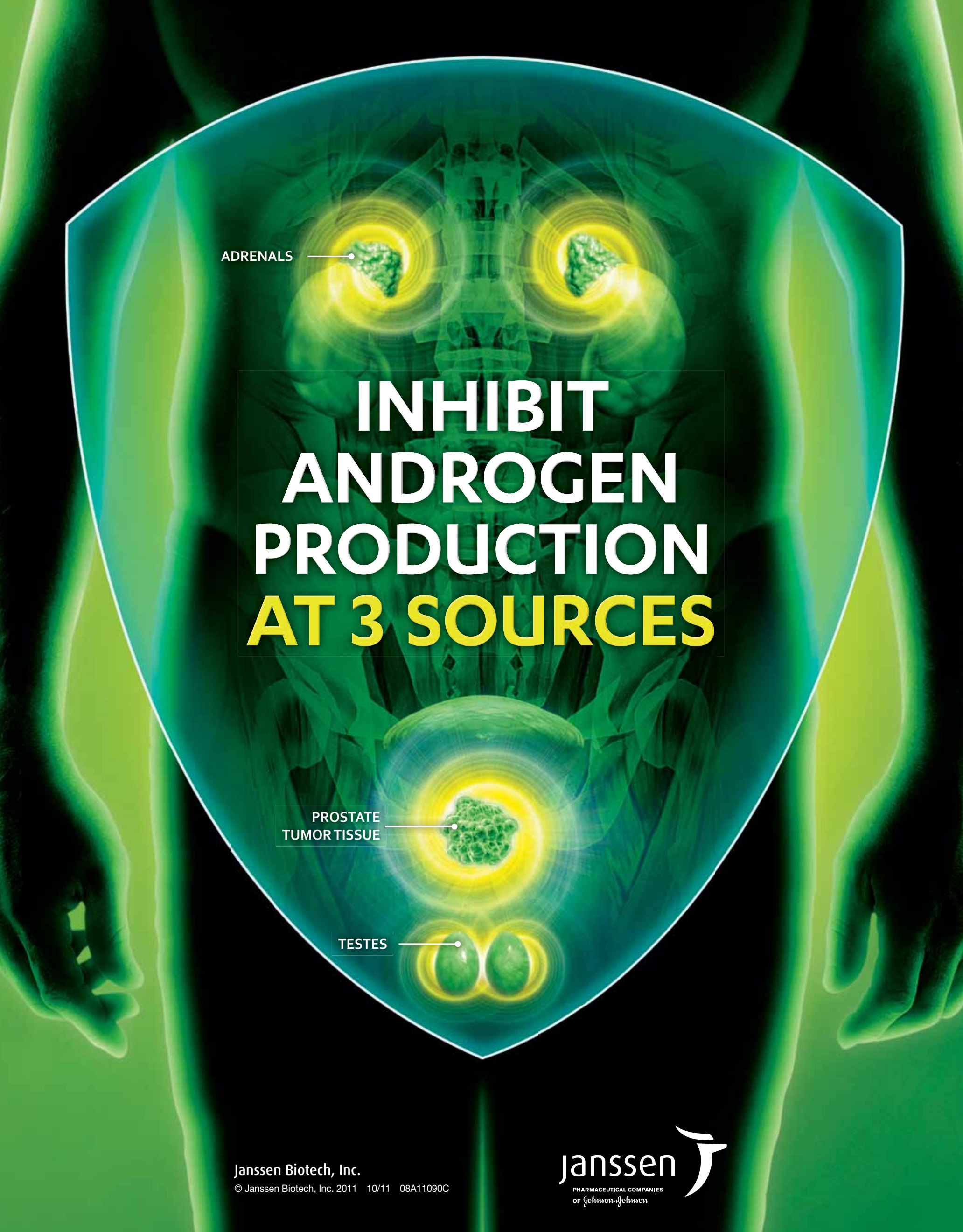
In an effort to make crizotinib more affordable and accessible, Pfizer is offering a copay assistance program that enables privately insured, eligible patients to pay no more than $100 per prescription.[8] It is important to note, though, that both the drug and copay assistance are only available at participating specialty pharmacies. The company is also offering its First Resource counselors to help uninsured or ineligible patients find other crizotinib-granting assistance programs.

Additionally, other treatments for ALK-positive NSCLC are currently under evaluation. A recent study identified 18 ALK-positive patients with an acquired resistance to crizotinib.[9] Recent papers have noted the efficacy of pemetrexed-based therapies[10] and ganetespib (a heat shock protein 90 inhibitor)[11] in treating the ALK subset. **EBO**

Funding Source: None.
Author Disclosure: The author reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.
Authorship Information: Acquisition of data; analysis and interpretation of data; and drafting of the manuscript.

Reference

1. Just P-A, Cazes A, Audebourg A, et al. Histologic subtypes, immunohistochemistry, FISH or molecular screening for the accurate diagnosis of ALK-rearrangement in lung cancer: a comprehensive study of caucasian non-smokers [published online ahead of print December 6, 2011]. *Lung Cancer*. Accessed January 27, 2012.
2. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene [published online ahead of print July 11, 2011]. *Nature*. 2007;448(7153):561-566. Accessed January 27, 2012.
3. Paik JH, Choi CM, Kim H, et al. Clinicopathologic implication of ALK rearrangement in surgically resected lung cancer: a proposal of diagnostic algorithm for ALK-rearranged adenocarcinoma [published online ahead of print November 28, 2011]. *Lung Cancer*. Accessed January 27, 2012.
4. Gene test for Pfizer cancer drug to cost $1,500 per patient. *Forbes* website. http://www.forbes.com/sites/matthewherper/2011/08/29/gene-test-for-pfizer-cancer-drug-to-cost-1500-per-patient/. Accessed February 1, 2012.
5. Solomon B, Bang Y-J, Camidge DR, et al. Timing of responses to crizotinib (PF-02341066) in anaplastic lymphoma kinase-positive patients with advanced non-small cell lung cancer. Paper presented at the 22nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics; November 16-19, 2010; Berlin, Germany. Accessed January 28, 2012.
6. Camidge DR, Bang Y-J, Iafrate AJ, et al. Clinical activity of crizotinib (PF-02341066) in ALK-posi-tive patients with advanced non-small cell lung cancer [Abstract 366PD]. Presented at the 35th European Society of Medical Oncology Congress; Milan, Italy; October 8-12, 2012. *Ann Oncol*.21(suppl 8):viii123.
7. Mitchell D. FDA approves lung cancer drug crizotinib, costs nearly $10K monthly. Emax-Health website. http://www.emaxhealth.com/1274/fda-approves-lung-cancer-drug-crizotinib-costs-nearly-10k-monthly. Published August 26, 2011. Accessed January 28, 2012.
8. Pfizer for Professionals (Pfizer Pro) website. http://pfizerpro.com/resources/minisites/xalkori_home/docs/PatientAssistance.pdf. Accessed January 29, 2012.
9. Katayama R, Shaw AT, Khan TM, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers [published online ahead of print June 25, 2012]. *Sci Transl Med* [abstract]. Accessed February 1, 2012.
10. Takeda M, Okamoto I, Sakai K, et al. Successful long-term treatment with pemetrexed of NSCLC associated with EML4-ALK and low thymidylate synthase expression [published online ahead of print November 6, 2011]. *Clin Lung Cancer*. Accessed February 1, 2012.
11. Jhaveri K, Taldone T, Modi S, Chiosis G. Advances in the clinical development of heat shock protein 90 (Hsp90) inhibitors in cancers [published online ahead of print October 29, 2011]. *Biochim Biophys Acta*. 2012;1823(3):742-755. Accessed January 29, 2012.



Janssen Biotech, Inc.

Janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

ZYTIGA® (abiraterone acetate) in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel.

ORAL THERAPY

once-daily

Zytiga®
(abiraterone acetate)
250 mg tablets

Mechanism of action

- Abiraterone is an *androgen biosynthesis inhibitor* (ABI) that directly affects the androgen biosynthesis pathway by inhibiting CYP17 (17α-hydroxylase/C17,20-lyase)
  - — Consequently, androgen biosynthesis is inhibited at 3 sources of testosterone production: the testes, adrenal glands, and prostate tumor tissue
- Androgen biosynthesis inhibition with ZYTIGA® results in decreased levels of serum testosterone and other androgens
- At the interim analysis of the pivotal phase 3 study, ZYTIGA® + prednisone showed a statistically significant improvement in median overall survival (OS) compared with the control arm*
  - — Median OS: 14.8 months vs 10.9 months (hazard ratio = 0.646; 95% confidence interval: 0.543, 0.768, $P < 0.0001$)

Important Safety Information

Contraindications—ZYTIGA® may cause fetal harm (Pregnancy Category X) and is contraindicated in women who are or may become pregnant.

Hypertension, Hypokalemia, and Fluid Retention Due to Mineralocorticoid Excess—Use with caution in patients with a history of cardiovascular disease or with medical conditions that might be compromised by increases in hypertension, hypokalemia, and fluid retention. ZYTIGA® may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Safety has not been established in patients with LVEF < 50% or New York Heart Association (NYHA) Class III or IV heart failure because these patients were excluded from the randomized clinical trial. Control hypertension and correct hypokalemia before and during treatment. Monitor blood pressure, serum potassium, and symptoms of fluid retention at least monthly.

Adrenocortical Insufficiency (AI)—AI has been reported in clinical trials in patients receiving ZYTIGA® in combination with prednisone, after an interruption of daily steroids, and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of AI if prednisone is stopped or withdrawn, if prednisone dose is reduced, or if the patient experiences unusual stress. Symptoms and signs of AI may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA®. Perform appropriate tests, if indicated to confirm AI. Increased dosages of corticosteroids may be used before, during, and after stressful situations.

Hepatotoxicity—Increases in liver enzymes have led to drug interruption, dose modification, and/or discontinuation. Monitor liver function and modify, withhold, or discontinue ZYTIGA® dosing as recommended (see Prescribing Information for more information). Measure serum transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] and bilirubin levels prior to starting treatment with ZYTIGA®, every two weeks for the first three months of treatment, and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the upper limit of normal (ULN) or the bilirubin rises above three times the ULN, interrupt ZYTIGA® treatment and closely monitor liver function.

Food Effect—ZYTIGA® must be taken on an empty stomach. Exposure of abiraterone increases up to 10-fold when abiraterone acetate is taken with meals. No food should be eaten for at least two hours before the dose of ZYTIGA® is taken and for at least one hour after the dose of ZYTIGA® is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state.

Use in Specific Populations—The safety of ZYTIGA® in patients with baseline severe hepatic impairment has not been studied. These patients should not receive ZYTIGA®.

Drug Interactions—ZYTIGA® is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration with CYP2D6 substrates that have a narrow therapeutic index. If an alternative cannot be used, exercise caution and consider a dose reduction of the CYP2D6 substrate. Additionally, abiraterone is a substrate of CYP3A4 *in vitro*. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution.

Adverse Reactions—The most common adverse reactions (≥ 5%) are joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection.

***Study Design:** ZYTIGA®, in combination with prednisone, was evaluated in a Phase 3, randomized, double-blind, placebo-controlled, multicenter study in patients with metastatic castration-resistant prostate cancer (mCRPC) who had received prior chemotherapy containing docetaxel (N = 1,195). Patients were randomized 2:1 to receive ZYTIGA® 1,000 mg orally once daily + prednisone 5 mg orally twice daily (n = 797) or placebo orally once daily + prednisone 5 mg orally twice daily (n = 398). Patients were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy and were at castration levels of testosterone (serum testosterone ≤ 50 ng/dL).[1] The primary efficacy endpoint was overall survival.*

Reference: 1. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.

Please see adjacent pages for brief summary of full Prescribing Information.

www.zytiga.com

ZYTIGA™ (abiraterone acetate)
Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

ZYTIGA in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel.

CONTRAINDICATIONS

Pregnancy: ZYTIGA may cause fetal harm when administered to a pregnant woman. ZYTIGA is contraindicated in women who are or may become pregnant. 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.

WARNINGS AND PRECAUTIONS

Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess: Use ZYTIGA with caution in patients with a history of cardiovascular disease. ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition *[see Adverse Reactions and Clinical Pharmacology (12.1) in full Prescribing Information]*. Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. The safety of ZYTIGA in patients with left ventricular ejection fraction <50% or NYHA Class III or IV heart failure has not been established because these patients were excluded from the randomized clinical trial. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

Adrenocortical Insufficiency: Adrenocortical insufficiency has been reported in clinical trials in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations *[see Warnings and Precautions]*.

Hepatotoxicity: Marked increases in liver enzymes leading to drug discontinuation or dosage modification have occurred *[see Adverse Reactions]*. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA treatment and closely monitor liver function. Re-treatment with ZYTIGA at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN *[see Dosage and Administration (2.2) in full Prescribing Information]*.

The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

Food Effect: ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state. The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

ADVERSE REACTIONS

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

Hypertension, hypokalemia, and fluid retention due to mineralocorticoid excess *[see Warnings and Precautions]*.

Adrenocortical insufficiency *[see Warnings and Precautions]*.

Hepatotoxicity *[see Warnings and Precautions]*.

Food effect *[see Warnings and Precautions]*.

Clinical Trial 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.

In a placebo-controlled, multicenter phase 3 clinical trial of patients with metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy, ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arm (N = 791). Placebo plus prednisone 5 mg twice daily was given to control patients (N = 394). The median duration of treatment with ZYTIGA was 8 months.

The most common adverse drug reactions (≥5%) reported in clinical studies were joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection.

The most common adverse drug reactions that resulted in drug discontinuation were aspartate aminotransferase increased, alanine aminotransferase increased, urosepsis and cardiac failure (each in <1% of patients taking ZYTIGA).

Adverse reactions and laboratory abnormalities related to mineralocorticoid effects were reported more commonly in patients treated with ZYTIGA than in patients treated with placebo: hypokalemia 28% versus 20%, hypertension 9% versus 7% and fluid retention (edema) 27% versus 18%, respectively (see Table 1). In patients treated with ZYTIGA, grades 3 to 4 hypokalemia occurred in 5% of patients and grades 3 to 4 hypertension was reported in 1% of patients *[see Warnings and Precautions]*.

Table 1 shows adverse reactions due to ZYTIGA that occurred with either a ≥ 2% absolute increase in frequency compared to placebo, or were events of special interest (mineralocorticoid excess, cardiac adverse reactions, and liver toxicities).

Table 1: Adverse Reactions due to ZYTIGA in a Placebo-Controlled Phase 3 Trial

	ZYTIGA with Prednisone (N=791)		Placebo with Prednisone (N=394)	
System/Organ Class Adverse reaction	All Grades[1] %	Grade 3-4 %	All Grades %	Grade 3-4 %
Musculoskeletal and connective tissue disorders				
Joint swelling/discomfort[2]	29.5	4.2	23.4	4.1
Muscle discomfort[3]	26.2	3.0	23.1	2.3
General disorders				
Edema[4]	26.7	1.9	18.3	0.8
Vascular disorders				
Hot flush	19.0	0.3	16.8	0.3
Hypertension	8.5	1.3	6.9	0.3
Gastrointestinal disorders				
Diarrhea	17.6	0.6	13.5	1.3
Dyspepsia	6.1	0	3.3	0
Infections and infestations				
Urinary tract infection	11.5	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	10.6	0	7.6	0
Renal and urinary disorders				
Urinary frequency	7.2	0.3	5.1	0.3
Nocturia	6.2	0	4.1	0
Cardiac disorders				
Arrhythmia[5]	7.2	1.1	4.6	1.0
Chest pain or chest discomfort[6]	3.8	0.5	2.8	0
Cardiac failure[7]	2.3	1.9	1.0	0.3

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
[5] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[6] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).
[7] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Cardiovascular Adverse Reactions: Cardiovascular adverse reactions in the phase 3 trial are shown in Table 1. The majority of arrhythmias were grade 1 or 2. Grade 3-4 arrhythmias occurred at similar rates in the two arms. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arm. No patients had sudden death or arrhythmia associated with death in the placebo arm. Cardiac ischemia or myocardial infarction led to death in 2 patients in the placebo arm and 1 death in the ZYTIGA arm. Cardiac failure resulting in death occurred in 1 patient on both arms.

Hepatotoxicity: Drug-associated hepatotoxicity with elevated ALT, AST, and total bilirubin has been reported in patients treated with ZYTIGA. Across all clinical trials, liver function test elevations (ALT or AST increases of > 5X ULN) were reported in 2.3% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. In the phase 3 trial, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5X ULN, or elevations in bilirubin > 3X ULN were observed, ZYTIGA was withheld or discontinued. In two instances marked increases in liver function tests occurred *[see Warnings and Precautions]*. These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40X ULN and bilirubin elevations 2 to 6 X ULN. Upon discontinuation of ZYTIGA, both patients had normalization of their liver function tests and one patient was re-treated with ZYTIGA without recurrence of the elevations.

In clinical trials, the following patients were excluded: patients with active hepatitis, patients with baseline ALT and/or AST ≥ 2.5X ULN in the absence of liver metastases, and patients with ALT and/or AST > 5X ULN in the presence of liver metastases. Abnormal liver function tests developing in patients participating in clinical trials were managed by treatment interruption, dose modification and/or discontinuation *[see Dosage and Administration (2.2) in full Prescribing Information and Warnings and Precautions]*. Patients with elevations of ALT or AST > 20X ULN were not re-treated.

Other Adverse Reactions: Adrenal insufficiency occurred in two patients on the abiraterone arm of the phase 3 clinical trial (< 1%).

Laboratory Abnormalities of Interest: Table 2 shows laboratory values of interest from the phase 3 placebo-controlled clinical trial. Grade 3-4 low serum phosphate (7.2%) and potassium (5.3%) occurred more frequently in the ZYTIGA arm.

Table 2: Laboratory Abnormalities of Interest in a Phase 3 Placebo-Controlled Clinical Trial

	Abiraterone (N=791)		Placebo (N=394)	
Laboratory Abnormality	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
High Triglyceride	62.5	0.4	53.0	0
High AST	30.6	2.1	36.3	1.5
Low Potassium	28.3	5.3	19.8	1.0
Low Phosphorus	23.8	7.2	15.7	5.8
High ALT	11.1	1.4	10.4	0.8
High Total Bilirubin	6.6	0.1	4.6	0

DRUG INTERACTIONS

Effects of Abiraterone on Drug Metabolizing Enzymes: ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Drugs that Inhibit or Induce CYP3A4 Enzymes: Based on *in vitro* data, ZYTIGA is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during ZYTIGA treatment *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category X *[see Contraindications]*. ZYTIGA is contraindicated in women who are or may become pregnant while receiving the drug. 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 and the potential risk for pregnancy loss. Women of childbearing potential should be advised to avoid becoming pregnant during treatment with ZYTIGA.

Nursing Mothers: ZYTIGA is not indicated for use in women. It is not known if abiraterone acetate 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 ZYTIGA, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use: ZYTIGA is not indicated in children.

Geriatric Use: Of the total number of patients in a phase 3 trial of ZYTIGA, 71% of patients were 65 years and over and 28% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients.

Patients with Hepatic Impairment: The pharmacokinetics of abiraterone were examined in subjects with baseline mild (n = 8) or moderate (n = 8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone after a single oral 1,000 mg dose of ZYTIGA increased by approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively compared to subjects with normal hepatic function.

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

The safety of ZYTIGA in patients with baseline severe hepatic impairment has not been studied. These patients should not receive ZYTIGA.

For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Patients with Renal Impairment: In a dedicated renal impairment trial, the mean PK parameters were comparable between healthy subjects with normal renal function (N=8) and those with end stage renal disease (ESRD) on hemodialysis (N=8) after a single oral 1,000 mg dose of ZYTIGA. No dosage adjustment is necessary for patients with renal impairment *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

OVERDOSAGE: There have been no reports of overdose of ZYTIGA during clinical studies. There is no specific antidote. In the event of an overdose, stop ZYTIGA, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and assess liver function.

Storage and Handling: Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP controlled room temperature]*. Based on its mechanism of action, ZYTIGA may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves *[see Use in Specific Populations]*.

Manufactured by:
Patheon Inc.
Toronto, Canada

Manufactured for:
Centocor Ortho Biotech Inc.
Horsham, PA 19044

Issued: April 2011

08Z11008

Forging a Pathway
(continued from Cover)

now known as Via Oncology Pathways, available to practices across the United States and internationally. To date, UPMC is the biggest customer of the commercial pathway service. The added contributions of external practices on the pathways committees are considered a valuable commodity, according to Kathy Lokay, president and chief executive officer of D3 Oncology Solutions, the UPMC affiliate that now owns and operates the Via Oncology Pathways. To date, practices in 11 states, India, and Ireland have purchased the Via Oncology Pathways, with many more in active discussions.

Peter Ellis, MD, director, Medical Oncology Network of UPMC Cancer Centers, explained that commercialization allows UPMC to leverage costs to expand the pathways to more cancer types, more modalities of care, and more phases of care. The pathway program, which initially focused on chemotherapy protocols for 3 or 4 diseases, has grown to include 95 percent of cancer incidences and now supports decisions surrounding prognostic testing, imaging, radiation therapy, and supportive care. In 2011, pathways were launched for gastric cancer, bladder cancer, and chronic myelogenous leukemia. The group plans to roll out a testicular cancer pathway this year.

Keys to Success

The success of UPMC's clinical pathway program is attributed to several operational and philosophical aspects.

Decision Support

In 2006, a software application was developed to provide real-time decision support via a user-friendly Web-based interface, referred to as the *pathway portal*. In effect, the software does the work of sorting through all the clinical algorithms for the physicians. The software also provides back-end information that serves as a valuable reporting source of user data, pathway adherence rates, and clinical trial accrual information.

Today, the pathway program is viewed as a software venture as much as it is a clinical content initiative. Lokay commented, "You can have all the best clinical content in the world, but if it sits on a shelf or a static website, you really don't have anything to show for it, nor are you really driving that decision support.

"With the growing complexity of cancer diagnosis, workup, and treatment in the age of personalized medicine, pathways are a critical tool to helping the typical community-based oncologist stay abreast of the data," explained Ellis. In anticipation of these impending challenges, Via Oncology Pathways recently updated its extensive IT platform. The transformed platform will allow them to manage and update thousands of branches.

Pathway Development and Review

Transparency throughout the pathway development process is maintained by (1) opening disease committees to all physicians within practices using the pathways, (2) providing evidence reviews that detail the data and rationale behind pathway decisions, and (3) adhering to a clear conflict of interest policy. "We take conflict of interest very seriously and we have positioned ourselves so that we have no dependency whatsoever on the pharmaceutical industry that would cause a conflict of interest, whether perceived or real," emphasized Lokay.

Thirty-three well-established disease committees—16 medical oncology committees and 17 radiation oncology committees—meet quarterly to review the pathways. Each committee is chaired by 2 physicians, 1 academic and 1 community-based. Separate medical oncology and radiation oncology committees operate for each disease, with 1 representative from each serving on the other's committee. While Via has not yet developed surgical pathways, surgeons serve on committees for several diseases, especially those for which surgery is integral to care.

The inclusion of academic doctors in the Via Oncology Pathway decision-making process is somewhat of a distinguishing practice. It is a long-standing philosophy of UPMC's pathway program that the process is best served by allowing the physicians who live by the pathways to design the pathways.

The disease committees strive to make evidence-based decisions whenever possible, but they do not adhere to a prescribed grading system. According to Brian Crandell, pathway pharmacist at Via Oncology Pathways, "We strive for the Phase III randomized trials, but unfortunately a lot of oncology drugs have been developed without a randomized trial against what is currently the standard of care." In these situations, the committee may turn to meta-analyses for guidance, combine trial evidence, or make consensus-based recommendations.

Decisions are based first on outcomes. If there is no clear winner in terms of outcomes, toxicity is evaluated. Cost is considered when there is no clear winner in terms of efficacy and toxicity. There are not many cases where it comes down to cost. "Usually you get to a point where you go, wow, okay, this regimen is much more toxic than the other one," said Lokay. In the absence of good data, the goal is to drive standardization.

UPMC is home to the University of Pittsburgh Cancer Institute, a nationally acclaimed and recognized research center. So, it is not surprising that clinical trials are held in high regard and positioned prominently in the Via Oncology Pathways. The decision support tool displays open clinical trials upstream of relevant treatment recommendations. Trial accruals are counted on pathway. If a physician does not accrue to the trial, they are asked to provide the reason for that decision from a structured list.

While much attention has been paid to the idea that UPMC, and now Via Oncology, adhere to a single treatment pathway model, this is often incorrectly interpreted to mean there is only 1 option or pathway for each disease. The reality is much more complex. The lung cancer pathways, for example, include 18 main branches with an additional 41 suboptions branching off of those.

The committees stratify each disease by a number of attributes such as stage, histology, molecular pathology, and others. They derive 1 single best treatment for the general presentation of each unique intersection of those attributes. This process is executed with the recognition that the single best treatment may work for approximately 60 percent of patients.

Next, they consider whether there are other subgroups of patients for whom that therapy is not going to be a good fit, for example, patients who have poor performance status, can't travel for weekly therapy, or have a contraindication to the primary treatment option. A subpathway is created for more commonly occurring profiles. Lokay clarified, "So, at the end of the day, for that node of the pathway, we may have 5 options, but 1 of those is considered the best for the more generalized population and the other 4 are suboptions for subpresentations. So, no, we don't have just 1, but we do try to drive to 1 single best as a first choice."

This approach allows solutions to be teased out when, from time to time, physicians call for more than 1 pathway option. Via believes that these requests are essentially the oncologists' way of saying they have different kinds of patients that they see and they need more than 1 option. Crandell explained, "There is a logic process the committee goes through…and it is just a matter of us figuring out how to explain that in the software, through questions or get-

ting the committee members to define more specifically when they would use each drug."

In the 2011 calendar year, UPMC surpassed its on-pathway adherence goal of 80 percent. On-pathway decisions are considered to be: (1) treatment decisions made according to pathway recommendation and (2) appropriate decisions to take the patient off pathway, for example, upon reaching the last line of treatment.

Why Pathways?

When asked about the benefits of pathways, Ellis answered, "Our message to oncologists is straightforward. Payers are demanding a solution to the rising costs of cancer. While technology is the primary driver, not physician fees, the physicians are caught in the middle." He went on to state, "It is imperative that physicians be the drivers of quality and cost containment for cancer, and if given the right tools for decision support and measurement, they can affect improvement far better than third-party intermediaries."

A recently published study, led by UPMC Cancer Centers investigators and Via Oncology Pathways, reported that implementation and auditing of clinical pathways promoted uniformity of care across both academic and community care centers.[4] In addition to reducing variability in care, pathways indirectly drive down cost by promoting the least toxic treatment options, according to Lokay. Detailing the benefits of UPMC pathways, Ellis mentioned the findings of 2 studies with Highmark Blue Cross Blue Shield, and 1 with IntrinsiQ, which demonstrate "a bending of the cost curve where the total cost of care for patients seen in pathways practices grows at a slower rate than the same costs for patients seen at non-pathways practices" (Table).

More recently, UPMC/Via Oncology has partnered with Highmark Blue Cross and Blue Shield, the oldest and largest healthcare plan in New Jersey, to operate a pilot project that supports and evaluates Via Oncology Pathways in 2 oncology practices in New Jersey. Preliminary cost analyses for the 2 pilot practices indicate successful results in terms of total cost of lung and breast cancer care for the pathway practices relative to non-pathway practices. Results from the project with Horizon

Table. Preliminary Cost Data From Highmark BCBS/UPMC Pathways Pilot Project[a]

	Growth Rate of Total Cost of Care (%)[b]	
	Breast Cancer	Non-small-cell Lung Cancer
Highmark/UPMC (60%)	7	1
Nonpathway Practice (40%)	16	6
Absolute Differential	9	5

[a]Analysis of Highmark claims data for breast cancer and non-small-cell lung cancer patients on active therapy.
[b]Two periods measured: 12 months before pathway implementation; 12 months after pathway implementation.

"Don't wait until the payers or referring physicians come to you…drive your own future success by leading with the right solution."

—Peter Ellis, MD
Director, Medical Oncology Network
UPMC Cancer Centers

THE AMERICAN JOURNAL OF MANAGED CARE

BCBSNJ are expected to be published later this year.

Early on, pathway proponents envisioned a scenario where payers who were benefitting from pathway-generated savings in drug- and hospital-related expenses would be willing to proactively contract around and support pathways. The reality is that payers generally have not taken an interest in funding new initiatives. While this may have been disappointing to some, Lokay sees it as a good thing. "If the payers are calling the shots on which pathways to buy/hire, I don't know how an oncology practice can cope in that world….I think we want practices picking the pathways they like and feel the most comfortable with."

The natural evolution has been that pathways have become a way for oncologists to demonstrate, "This is the way we care for our patients, *all* of our patients." Along those lines, practices are using pathways to forestall payers from introducing measures such as rate cuts, prior authorization, or specialty pharmacy.

Health reform vehicles such as medical homes and accountable care organizations are a big factor in why more practices have started looking at pathways programs. Practices are investing in and adopting pathways to better position themselves in their local market. To some extent, practices use pathways to demonstrate that their patients are receiving evidence-based and personalized care that takes into account things like toxicity and cost. "We have a number of practices that are jockeying to make sure that they either keep all their existing referral sources or maybe actually in the process grow their referral sources by attracting primary care medical home docs," said Lokay.

What does the future hold for the pathway program at UPMC? Dr Ellis offered his insights: "We are already on track to achieve the vision of pathways that integrate seamlessly with the major electronic medical records and cover virtually all cancer types, phases of care, and modalities of care. We see the pathways being chosen by the practices, not the payers! We see the ability to measure outcomes that prove that standardization to the best evidence-based medicine improves patient outcomes and reduces costs." **EBO**

"If the payers are calling the shots on which pathways to buy/hire, I don't know how an oncology practice can cope in that world."

—Kathy Lokay
President and chief executive officer
D3 Oncology Solutions

Funding Source: None.

Author Disclosure: The author reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

References

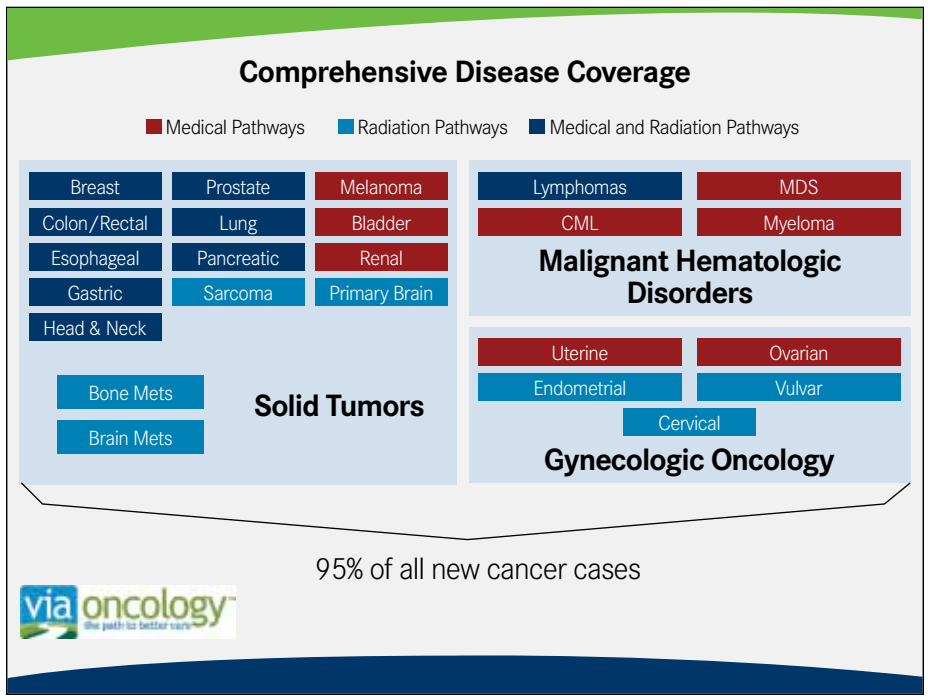
1. Holcombe D. Clinical pathways programs: confusing choices for payers and physicians: part 1: selecting the appropriate pathways program. *JOMCC*. 2010;3(5):10-11.

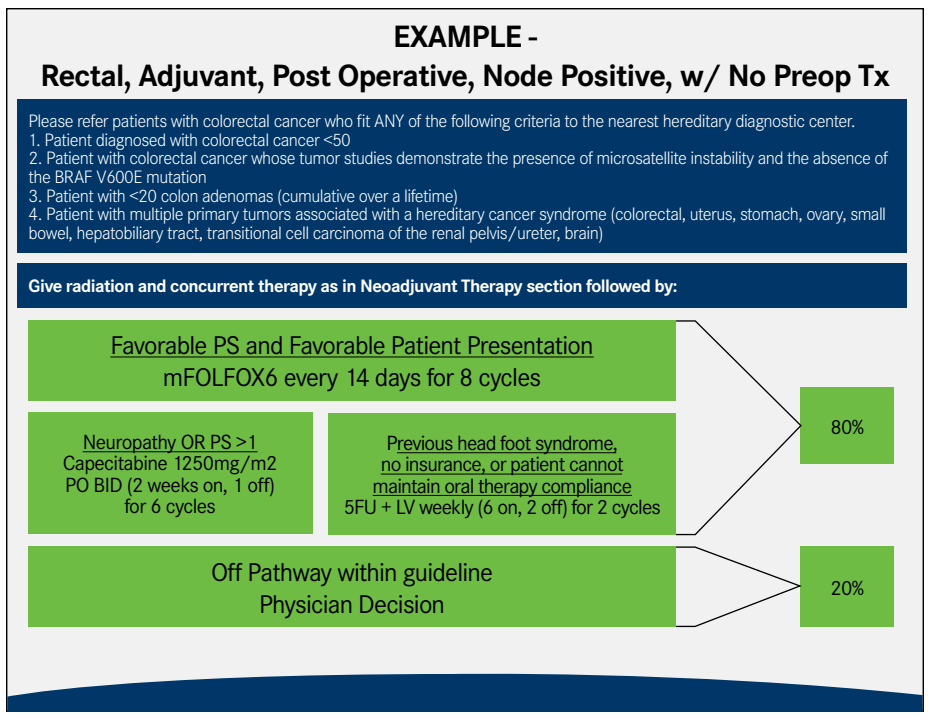
2. Hoverman JR, Cartwright TH, Patt DA, et al. Pathways, outcomes, and costs in colon cancer: retrospective evaluations in two distinct databases. *J Oncol Pract*. 2011;7(suppl 3):52S-59S.

3. Neubauer MA, Hoverman JR, Kolodziej M, et al. Cost-effectiveness of evidence-based treatment guidelines for the treatment of non-small-cell lung cancer in the community setting. *J Oncol Pract*. 2010:6(1):12-18.

4. Beriwal S, Rajagopalan MS, Flickinger JC, Rakfal SM, Rodgers E, Heron DE. How effective are clinical pathways with and without online peer-review? an analysis of bone metastases pathway in a large, integrated national cancer institute-designated comprehensive cancer center network [published online ahead of print January 13, 2012]. *Int J Radiat Oncol Biol Phys*. doi:10.1016/ijrobp.2011.09.056.

5. Ellis PG. All pathways are not created equal. *Oncology Times*. 2010;32(10):46-48. doi:10.1097/01.COT.0000381228.24720.6b.





According to Dr Peter Ellis, oncology groups considering pathways should ask the following questions when evaluating their options[5]:

1. Who develops the pathways?
2. What is the pathway development process?
3. Do the pathways define 1 best treatment for each state and stage of disease?
4. Are the pathways comprehensive?
5. How detailed are the pathways?
6. How often are the pathways updated?
7. Do the pathways support clinical trials?
8. What is the quality of the decision support tools that accompany the pathways; for example, are they available in real time at point of care?
9. Are meaningful reports provided from pathway usage data?
10. What is the reputation and business forecast of the organization developing the pathways?
11. What do your colleagues think about the various pathway options?

Prostate Cancer

Jennifer Klemm, PhD; and Stanton R. Mehr

Prostate cancer is the most prevalent non-cutaneous malignancy among men, accounting for over 240,000 new diagnoses each year in the United States.[1] Because of its indolent nature and the excellent curative options for early-stage disease, prostate cancer deaths are more modest, occurring in fewer than 34,000 men each year.[1] According to estimates from the American Cancer Society, the 5-year survival for patients with prostate cancer is almost 100%, and the 10-year survival is 91%.[2]

In a significant portion of patients, prostate cancer progresses very slowly or poses limited danger. Therefore, it is sometimes said that "more people die with prostate cancer than of prostate cancer." Conservative approaches to treatment for patients with indolent prostate disease often include little more than periodic monitoring with prostate-specific antigen (PSA) testing.

Even patients with indolent prostate cancer often choose active treatment approaches, which can include surgery or radiation therapy followed by hormonal therapy, which essentially reduces testosterone to post-castration levels. In patients with active disease, this approach prolongs survival, but in a proportion of these patients, the disease will progress. Once patients reach this advanced stage, called metastatic castrate-resistant prostate cancer (CRPC), the disease is no longer indolent, having a median survival of only 16 to 20 months.[3,4] For these patients and the healthcare system, the question of value is more of a consideration.

Nearly 2.36 million American men are estimated to have prostate cancer,[5] and the total cost of caring for these patients has been estimated to be $9.86 billion.[6] Approximately 10% to 20% of these men will develop CRPC within 5 years of diagnosis.[7] In 1 health economic study of CRPC patients, the total per patient prostate cancer–related costs were $21,588 annually.[8] In another study, performed in 2006 prior to the approval of the 4 most recent agents, the mean costs for the last year of life were $33,691.[6] Current costs are almost certainly significantly greater.

Current Treatment Options

For patients who have metastatic CRPC, metastases are most often found in the bone, with 1 study reporting that 84% of all patients with CRPC have bone metastases upon diagnosis.[9] These patients generally receive either the bisphosphonate zoledronic acid or the more recently approved targeted agent denosumab to prevent or delay skeletal-related events (SREs) associated with bone metastases.[10] Radiation therapy may also be used to control bone pain, and surgical intervention is sometimes necessary as well. In addition to these palliative treatments, the active treatments described below are prescribed, depending on whether these patients are currently experiencing symptoms or not.

For asymptomatic metastatic CRPC patients, the National Comprehensive Cancer Network recommends treatment with 1 course (3 doses) of sipuleucel-T (Provenge),[10] the first therapeutic vaccine to be approved by the US Food and Drug Administration (FDA) and which has been shown to produce a survival advantage of 4.1 months.[11] Asymptomatic patients are also often treated with secondary hormonal therapy, such as ketoconazole or an antiandrogen, although no survival benefit has ever been established for this approach.

Once patients develop symptomatic disease, they generally receive treatment with the chemotherapeutic agent docetaxel (Taxotere), which has demonstrated a survival advantage of 2.4 months.[12] After failure of docetaxel, several options exist, including (1) the targeted hormonal agent abiraterone acetate (Zytiga), providing a survival benefit of 3.9 months,[13] (2) another chemotherapy agent, cabazitaxel (Jevtana), providing a survival benefit of 2.4 months,[14] (3) docetaxel rechallenge, and (4) secondary hormonal therapy.

Economics

All of the above-outlined, recently approved treatment options for CRPC patients come at a high price tag. Sipuleucel-T is the most expensive therapy, costing $93,000 for a full course, but only 1 course of therapy is given to each patient. The average wholesale price of cabazitaxel is $9600 for 1 course of treatment, with a median of 6 courses given in the pivotal trial, for a median total of $57,600 per patient.[15] Abiraterone costs $5000 per month and the average duration of treatment in its pivotal trial was 8 months, for an average total of $40,000 per patient.[13]

Abiraterone has the additional challenge of being an oral drug, which is often covered (or not covered) under a patient's pharmacy benefit rather than as a medical benefit. Because prescription drug coverage is typically less generous than medical coverage, patients prescribed oral targeted agents often find themselves responsible for paying thousands of dollars in coinsurance. Thus, the amount of patient out-of-pocket costs often becomes the deciding factor in treatment choice, with patients often forgoing life-prolonging therapy due to the high cost of the drug.

For the prevention of SREs, the cost of denosumab is $1650 per dose, compared with $844 for zoledronic acid,[16,17] but the drug acquisition costs are not the only considerations when determining overall cost-effectiveness. Because denosumab is administered via subcutaneous injection rather than intravenous infusion, it saves both chair time and infusion costs relative to zoledronic acid. In addition, denosumab avoids 0.11 SREs per year in patients with CRPC.[15] In 1 health economic study, when all costs were considered, including the cost of avoided SREs, denosumab was associated with a $51,319 incremental increase per SRE avoided over a 3-year period in this patient population.[15] Based on a willingness-to-pay threshold of $70,000 per SRE avoided, denosumab was cost-effective in nearly 50% of cases at 1 year and 79% of cases at 3 years.[15]

Additional Drivers of the Cost of Care

According to 1 analysis, costs incurred by patients with CRPC are greatest in the 6 months preceding death because of home-care services, hospitalization, and palliative-care costs.[18] This analysis was conducted before the advent of the newer, more expensive drugs now available for the treatment of CRPC. In the current landscape, drug costs are certain to be a formidable driver of costs. However, unlike many therapies in the past, these drugs produce a survival advantage, making them potentially a good value despite their high cost.

In a recently published health economic study of patients with prostate cancer, ambulatory costs were determined to be the main driver of the cost of care, accounting for 57% of the total costs.[8] Ambulatory costs were those incurred during physician office visits and visits at outpatient facilities, such as outpatient procedures and services (eg, laboratory work, radiology services). The next most costly driver of the cost of care for patients with CRPC was inpatient costs, absorbing 30% of the total costs. Pharmacy costs accounted for less than 10% of the total cost, and emergency department costs were negligible. **EBO**

"There is a great deal of evidence to support that PSA testing is not a sensitive tool for determining the aggressiveness of prostate cancer, but at the same time it is a readily available and accepted test by PCPs..."

—Kenneth Schaecher, MD
Medical Director
SelectHealth

THE AMERICAN JOURNAL OF MANAGED CARE

Funding Source: None.

Author Disclosures: Mr Mehr reports receiving payment for involvement in the preparation of this article. Dr Klemm reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (JK); acquisition of data (SRM); analysis and interpretation of data (SRM); drafting of the manuscript (JK, SRM); and critical revision of the manuscript for important intellectual content (JK, SRM).

References

1. American Cancer Society. *Cancer Facts & Figures 2011*. Atlanta: American Cancer Society; 2011.

2. American Cancer Society. What are the key statistics about prostate cancer? http://www.cancer.org/Cancer/ProstateCancer/DetailedGuide/prostate-cancer-survival-rates?docSelected=prostate-cancer-key-statistics. Accessed January 5, 2012.

3. James ND, Caty A, Payne H, et al. Final safety and efficacy analysis of the specific endothelin A receptor antagonist zibotentan (ZD4054) in patients with metastatic castration-resistant prostate cancer and bone metastases who were pain-free or mildly symptomatic for pain: a double-blind, placebo-controlled, randomized Phase II trial. *BJU Int.* 2010;106(7):966-973.

4. Kantoff PW, Schuetz TJ, Blumenstein BA, et al. Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2010;28(7):1099-1105.

5. Cancer prevalence: how many people have cancer? American Cancer Society website. http://www.cancer.org/cancer/cancerbasics/cancer-prevalence. Accessed January 2, 2012.

6. Roehrborn CG, Black LK. The economic burden of prostate cancer. *BJU Int.* 2011;108:806-813.

7. Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. *Int J Clin Pract*. 2011;65(11):1180-1192.

8. Alemayehu B, Buysman E, Parry D, Becker L, Nathan F. Economic burden and healthcare utilization associated with castration-resistant prostate cancer in a commercial and Medicare Advantage US patient population. *J Med Econ*. 2010;13(2):351-361.

9. Inoue T, Segawa T, Kamba T, et al. Prevalence of skeletal complications and their impact on survival of hormone refractory prostate cancer patients in Japan. *Urology*. 2009;73(5):1104-1109.

10. NCCN Clinical Practice Guidelines in Oncology. Prostate cancer. V4.2011. National Comprehensive Cancer Network website. http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed January 2, 2012.

11. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363(5):411-422.

12. Tannock IF, de WR, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502-1512.

13. de Bono JS, Logothetis CJ, Molina A, et al.

Payer Perspective

Interview with Kenneth Schaecher, MD

***EBO*: Prostate cancer is a bit unusual as a carcinoma because it is either aggressive or very slow growing and there are a number of options to treat it (eg, surgical resection, cryotherapy, radiologic therapy, chemotherapy, immunomodulatory treatment). How do health plan efforts to help patients make choices that are most appropriate for them provide value?**

Dr Schaecher: Helping patients make the choice that is right for them is a challenge because of the fragmented nature of the sites of care for prostate cancer. Urologists attempt to provide counseling but their bias is to do surgery, and patients may be unintentionally steered in that direction. Patients themselves let their own biases choose therapies. For example, they may decide on proton-beam therapy, based on marketing, rather than other forms of radiation therapy, which are equally efficacious but much less costly.

Our health plan is embarking on "shared decision-making" pilots around this area, in an effort to help patients objectively wade through the volume of information on the various treatment modalities in an objective and organized manner free of individual provider or marketing biases. These shared decision-making tools will be available at both specialty care sites and primary care offices for patients diagnosed with prostate cancer and working through the decision process as to how they wish to proceed with treatment.

***EBO*: What is your view on prostate-specific antigen (PSA) testing and its ability to stratify patients at risk for aggressive malignancy?**

Dr Schaecher: The role of PSA testing has become more controversial, given the recent recommendations of the US Preventive Services Task Force to discontinue use of this test as a means to screen for prostate cancer. This recommendation was based upon their review of a number of studies but especially 2 large studies that showed the harms from this testing likely outweighed the benefits.

This recommendation has not been universally supported by urologists and some other practitioners, as they feel PSA testing has some benefit when used in conjunction with a digital rectal exam of the prostate and when viewed serially over time rather than as a single value.

From a payer perspective, I believe there is increased skepticism regarding the value of PSA testing as it is primarily being performed by primary care physicians (PCPs) and they remain for the most part uninformed about the nuances of this testing. There is a great deal of evidence to support that PSA testing is not a sensitive tool for determining the aggressiveness of prostate cancer, but at the same time it is a readily available and accepted test by PCPs and thus is used.

***EBO*: How strong a role does your organization's medical technology assessment group play in policy making for prostate cancer treatments (versus a Pharmacy & Therapeutics [P&T] Committee)?**

Dr Schaecher: It depends on the treatment. Drugs are typically assessed by a P&T Committee whereas other treatments like surgical procedures, radiation, or cryotherapy are evaluated by the Technology Assessment Committee. There can be some overlap in committee function should there be a pharmaceutical treatment that is administered by some unique device. In that circumstance, the technology assessment committee would take the lead and present its final determination to P&T for notification and discussion.

***EBO*: Does your health plan cover the Provenge vaccine?**

Dr Schaecher: We do cover Provenge, but we apply prior authorization that is specific to the FDA labeling.

***EBO*: Do you believe that therapeutic vaccines like Provenge will provide an avenue to good value in prostate cancer treatment?**

Dr Schaecher: Therapeutic vaccines have the potential to offer an alternative treatment for patients who have failed alternative therapies and perhaps over time an earlier line of therapy. However, the word "value" is pejorative. Is this clinical "value" or financial "value"? At the current price points set for Provenge, it doesn't seem to offer significant financial value, though it may offer limited clinical value. The failure of urologists and medical oncologists to embrace this therapy as evidenced by its slow update may also speak to residual questions regarding the clinical value of this particular therapy, but I don't think it is a statement regarding therapeutic vaccinations in general.

From a health plan perspective, Provenge is not felt to be of value based on its current pricing and the fact that it offers limited clinical benefit based on current clinical studies.

***EBO*: What do you believe is the most exciting area for pipeline research in prostate cancer?**

Dr Schaecher: Immune system modulation—whether it be through therapeutic vaccine or biologic therapy—is the area that has the greatest "mojo" at present. Given that for many patients, prostate cancer is an indolent disease that has characteristics which are more akin to a chronic immune state like lupus, rheumatoid arthritis, or multiple sclerosis, engaging a targeted approach that helps the immune system identify and eliminate aberrant cell lines shows significant promise in treating this condition.

Dr Schaecher is medical director, SelectHealth, based in Salt Lake City, Utah.

Additional Suggested Reading

Stokes ME, Ishak J, Proskorovsky I, Black LK, Huang Y. Lifetime economic burden of prostate cancer. *BMC Health Serv Res*. 2011;11(1):349.
A model was developed to estimate the lifetime costs of patients with prostate cancer; the authors found that this averaged $34,400.

Park S, Kim SC, Kim W, Song C, Ahn H. Impact of adjuvant androgen-deprivation therapy on disease progression in patients with node-positive prostate cancer [published online ahead of print November 17, 2011]. *Korean J Urol*. 2011;52(11):741-745.
Adjuvant androgen-deprivation therapy patients with metastatic prostate cancer did not reduce or delay disease progression or improve survival, according to this research from South Korea, raising doubts about the value of this therapeutic intervention.

Chou R, Dana T, Bougatsos C, et al. *Treatments for Localized Prostate Cancer: Systematic Review to Update the 2002 U.S. Preventive Services Task Force Recommendation* [Internet]. Rockville, MD: Agency for Healthcare Research and Quality (US); October 2011:Publication No. 12-05161-EF-1.
This comprehensive review of evidence-based data demonstrates that for patients with early, localized prostate cancer, virtually any active intervention has important adverse effects. Based primarily on cohort studies, treating approximately 3 men with prostatectomy, 7 men with radiation therapy, or 2 to 3 men with androgen deprivation therapy instead of watchful waiting would each result in 1 additional case of erectile dysfunction, and treating approximately 5 men with prostatectomy would result in 1 additional case of urinary incontinence (in addition to perioperative mortality or other complications).

Lin K, Croswell JM, Koenig H, Lam C, Maltz A. *Prostate-Specific Antigen-Based Screening for Prostate Cancer: An Evidence Update for the U.S. Preventive Services Task Force* [Internet]. Rockville, MD: Agency for Healthcare Research and Quality (US); October 2011:Publication No. 12-05160-EF-1.
In this updated review, the reviewers find that after about 10 years, PSA-based screening results in the detection of more cases of prostate cancer, but small to no reduction in prostate cancer–specific mortality.

Allan GM, Chetner MP, Donnelly BJ, et al. Furthering the prostate cancer screening debate (prostate cancer specific mortality and associated risks). *Can Urol Assoc J*. 2011;5(6):416-421.
In high-quality studies of prostate cancer screening (particularly prostate-specific antigen), there is good evidence that prostate cancer mortality is reduced. However, the risks associated with prostate cancer screening (including a 70% false-positive rate and adverse events associated with biopsy) are considerable and must be weighed against the advantage of reduced cancer-specific mortality.

Godbole AM, Njar VC. New insights into the androgen-targeted therapies and epigenetic therapies in prostate cancer [published online ahead of print October 12, 2011]. *Prostate Cancer*. 2011;2011:918707.
A review of the findings about the antiandrogens and the epigenetic factors that modulate the action of androgen receptors in patients with prostate cancer.

Swanson GP, Quinn D. Using molecular markers to help predict who will fail after radical prostatectomy [published online ahead of print April 14, 2011]. *Prostate Cancer*. 2011;2011:290160.
Recent phase III trial data clearly demonstrate that adjuvant therapy can reduce recurrence and increase survival after prostatectomy for prostate cancer. There is great interest in being able to accurately predict who is at risk of failure, to avoid treating those who may not benefit. This is a comprehensive review of the current status of molecular markers in predicting patient outcome after radical prostatectomy.

Bitting RL, Armstrong AJ, George DJ. Management options in advanced prostate cancer: what is the role for sipuleucel-T [published online ahead of print October 20, 2011]? *Clin Med Insights Oncol*. 2011;5:325-332.
Authors from the Duke Cancer Institute provide a review of the clinical trial data leading to the approval of sipuleucel-T and the implications for optimal management and sequencing of treatment in this patient population.

Engel-Nitz NM, Alemayehu B, Parry D, Nathan F. Differences in treatment patterns among patients with castration-resistant prostate cancer treated by oncologists versus urologists in a US managed care population [published online ahead of print July 4, 2011]. *Cancer Manag Res*. 2011;3:233-245.
Patients with castration-resistant prostate cancer who were treated by oncologists had greater use of hormones, chemotherapy, and radiation; higher percentages of patients with inpatient stays, emergency department, and ambulatory visits; and higher healthcare costs, than patients treated by urologists.

Prostate cancer trends. Centers for Disease Prevention and Control website. http://www.cdc.gov/cancer/prostate/statistics/trends.htm. Accessed January 5, 2012.
The CDC offers state-by-state prevalence, ethnic, and age-related risk information on prostate cancer.

***Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer*. Agency for Healthcare Research and Quality. http://www.effectivehealthcare.ahrq.gov/ehc/products/9/79/2008_0204ProstateCancerExecSum.pdf. Accessed January 5, 2011.**
Part of AHRQ's Effective Health Care Program on comparative-effectiveness research, this monograph spells out the evidence on watchful waiting, cryoablation, prostatectomy, radiotherapy, high-intensity ultrasound, and brachytherapy for the management of localized prostate cancer.

"Helping patients make the choice that is right for them is a challenge because of the fragmented nature of the sites of care for prostate cancer."

—Kenneth Schaecher, MD
Medical Director
SelectHealth

Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.

14. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010;376(9747):1147-1154.

15. Xie J, Namjoshi M, Wu EQ, et al. Economic evaluation of denosumab compared with zoledronic acid in hormone-refractory prostate cancer patients with bone metastases. *J Manag Care Pharm*. 2011;17(8):621-643.

16. FDA approves Amgen's XGEVA(TM) (denosumab) for the prevention of skeletal-related events in patients with bone metastases from solid tumors [press release]. Amgen website. http://www.amgen.com/media/media_pr_detail.jsp?releaseID=1498709. Accessed January 5, 2012.

17. Amgen's Xgeva hits resistance over cost-benefit debate. *Wall Street Journal*. April 5, 2011.

18. Krahn MD, Zagorski B, Laporte A, et al. Healthcare costs associated with prostate cancer: estimates from a population-based study. *BJU Int*. 2010;105(3):338-346.

Patient Assistance NO

Our Patient Assistance Now Oncology (PANO) Web site makes it easy with all-in-one convenience providing simplicity, efficiency, and better access for you, your patients, and your oncology practice managers (OPMs).

Let's Get Started!

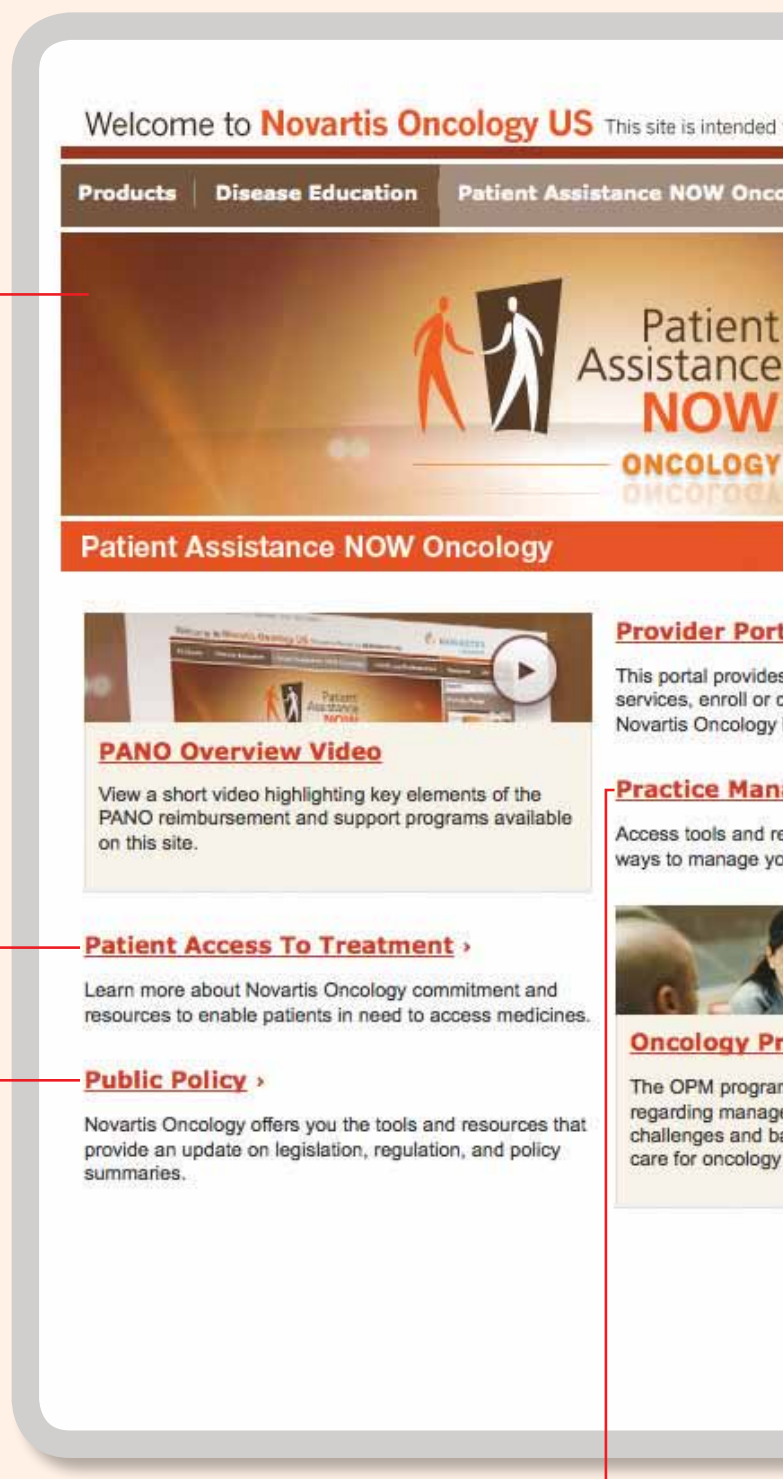
The Patient Assistance NOW Oncology (PANO) Web site offers quick and easy navigation to information about the broad array of reimbursement and support programs available to your patients.

For Patient Care

A link to our central hub of patient access resources, where you will find tools for insurance verification, assistance with identifying alternate sources of coverage/funding that may assist with patient costs, assistance for low-income and uninsured patients, and more.

What's New in Healthcare Reform?

Links to information about the ever-changing landscape of healthcare reform, guideline requirements, Medicare, and drug purchasing options.



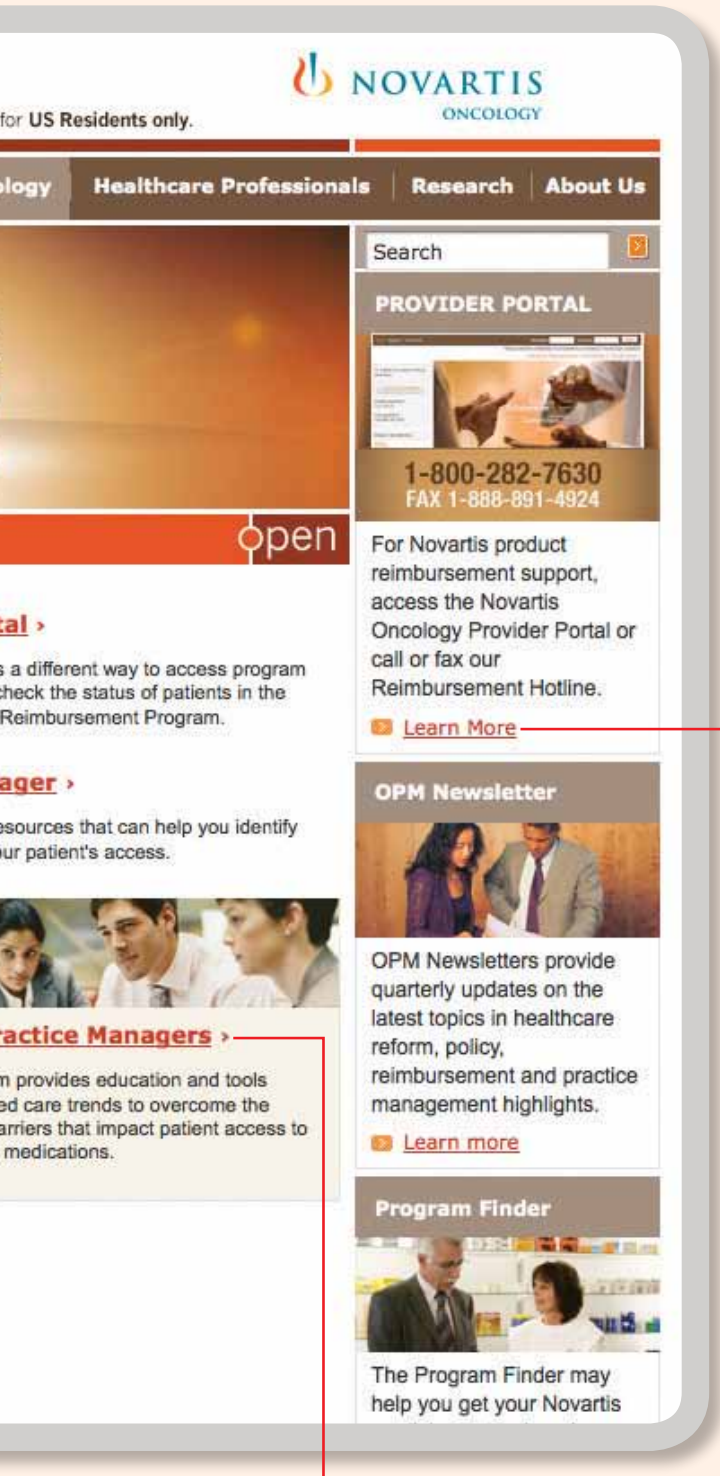
Patient Access SOS

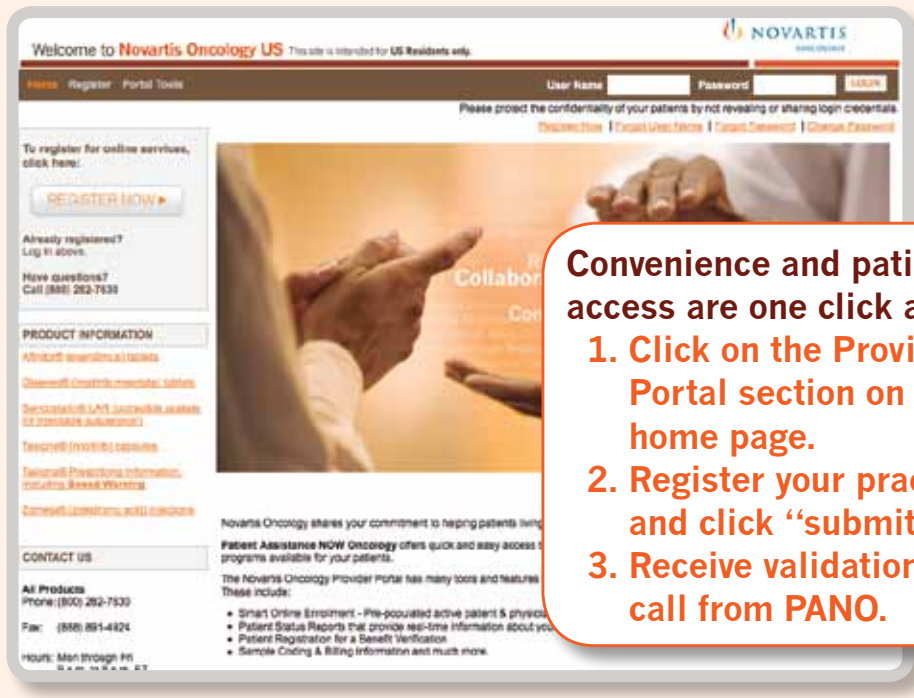
Find pertinent information to help support your patients, including details on quality measures, e-prescriptions, and Medicare Administrative Contractor (MAC) and Recovery Audit Contractor (RAC) tools.

Brought to you by the publisher of

THE AMERICAN JOURNAL OF MANAGED CARE

OW Oncology Mapped!®





Convenience and patient access are one click away:

1. Click on the Provider Portal section on the home page.
2. Register your practice and click "submit."
3. Receive validation phone call from PANO.

What Can the Provider Portal Do for Me?

- Enroll a new patient or check the status of a current patient
- Organize patient reports tailored to meet your needs
- See a listing of all your patients as soon as you enter the portal
- Get immediate alerts that highlight important tasks and events to expedite patient treatment
- Download forms
- Click on a patient's name to instantly display that patient's information
- Attach a document to a patient's electronic file (as easy as adding an attachment to an e-mail)
- Manage your individual user profile and easily change your contact information

A Program Just for OPMs

A link to an OPM program that provides education and tools

- Managed care trends
- Overcoming challenges and barriers that impact patient access
- Link to e-slide library

Patient Assistance NOW Oncology
www.OncologyAccessNow.com

Patient Assistance NOW Oncology Hotline:
1-800-282-7630

Patient Assistance NOW ONCOLOGY

Helping to make access to therapies easier

NOVARTIS ONCOLOGY

Printed in U.S.A October 2011 PAN-1032003

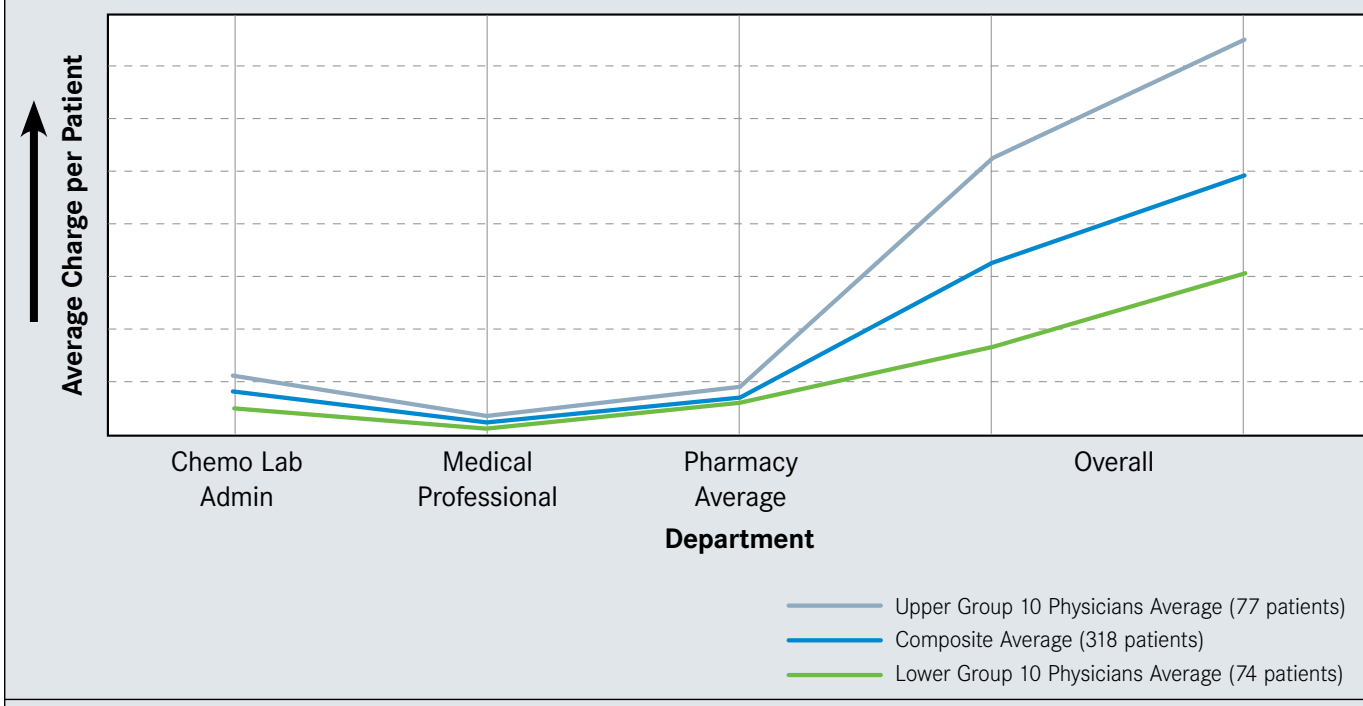
Value-Based Reimbursement
(continued from Cover)

choices should empower us to make wise decisions in healthcare. It allows us to maximize value. And to the extent that we can improve outcomes, it allows us to improve quality of care. Since the healthcare dollar has finite limits, objective, evidence-based treatment should help us do better with the dollars available.

Sadly, ample evidence suggests we have far to go. The best marker of how far short we are falling is the regional variability in healthcare spend. Seniors in Minneapolis cost Medicare $3341 per year whereas in Miami, they cost Medicare $8881 per year, 2½ times as much.[3] These variations are even more exaggerated when care during the last 6 months of life is analyzed. The data from the Dartmouth Atlas are most compelling.[4] Utilization of all healthcare services, including hospital days, ICU days, and doctors visits, goes up. But what is most alarming is the variability from state to state and from region to region. For example, hospital days in the last 6 months range from 7 in Utah and Oregon to almost 16 in DC and almost 12 in Florida. Office visits follow the same trends. Not unexpectedly, hospice enrollment follows an inverse relationship. Without question, socioeconomic factors explain some of the variability and there is no clear "quality standard" which allows definition of an appropriate benchmark. However, this much variability cannot be viewed as good.

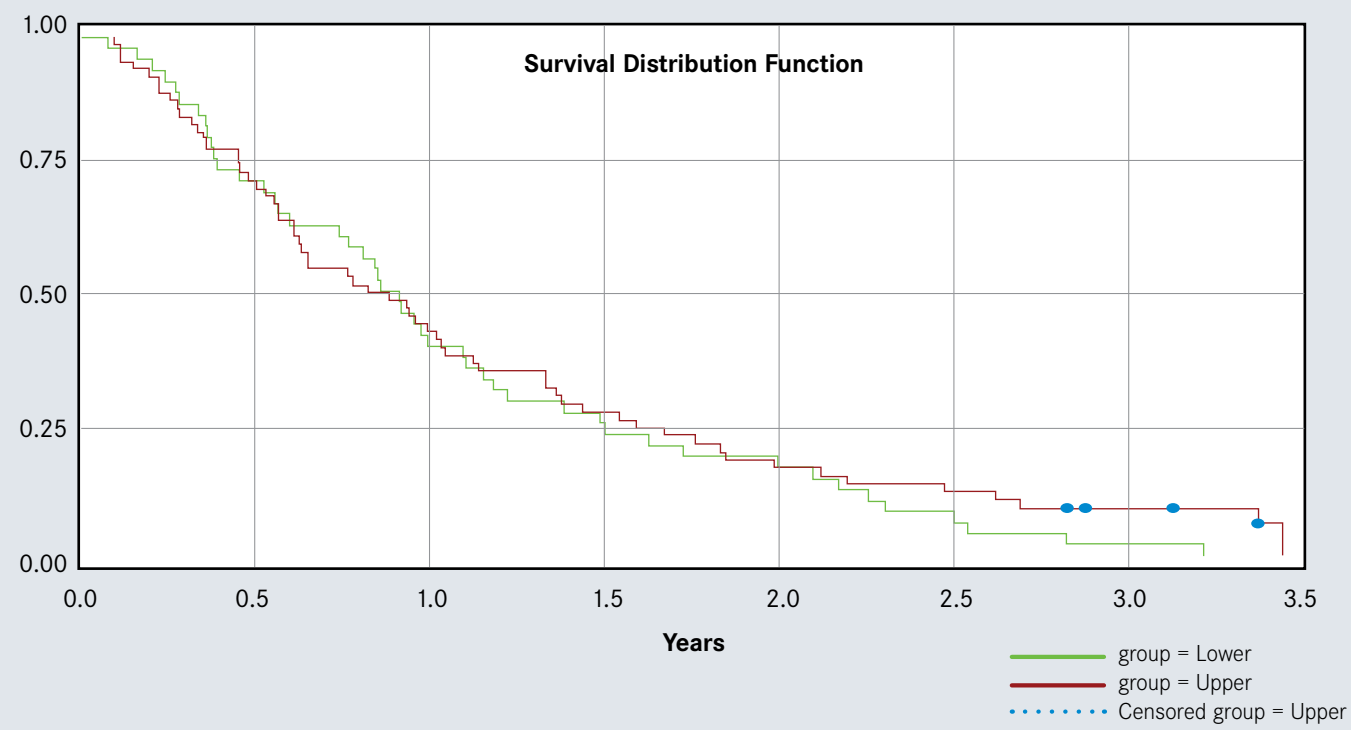
This type of variability certainly occurs in oncology care, even on a much smaller scale. Our studies looking at charges for lung cancer therapy within a single large practice shows wide interphysician differences.[5] Notably, spend was not correlated at all with better survival (**Figures 1A and 1B**). Patients cared for by the most expensive doctors did just as well (or just as poorly) as those cared for by the most thrifty doctors. In oncology, the spend is spread among several services and even several sites of service. Although there are some publications based on Surveillance, Epidemiology, and End Results data in the

Figure 1A. Segregation of Charges by Department, Age <65 Years



Reprinted from Hoverman and Robertson.[5]

Figure 1B. Survival: Extensive NSCLC, *P* = .99

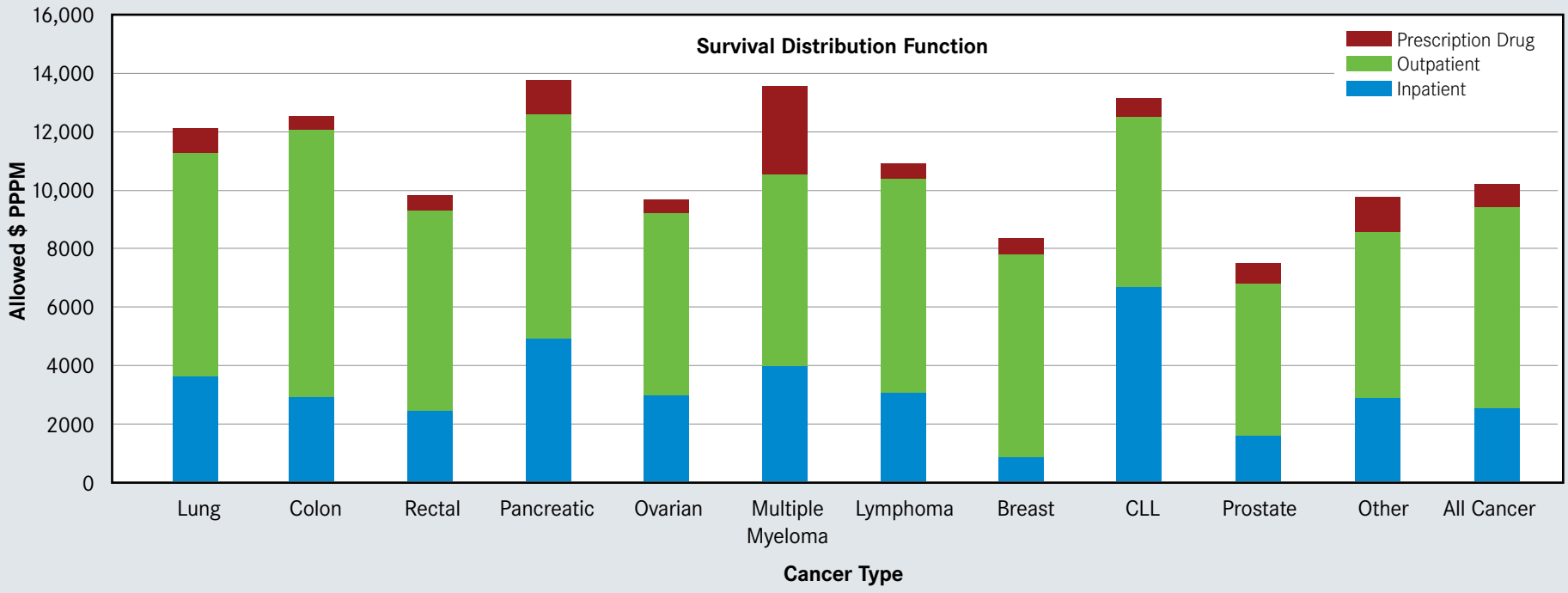


NSCLC indicates non-small cell lung cancer.
Reprinted from Hoverman and Robertson.[5]

"Patients cared for by the most expensive doctors did just as well (or just as poorly) as those cared for by the most thrifty doctors."

—Michael Kolodziej, MD, and J. Russell Hoverman, MD, PhD
US Oncology

Figure 2. Cost of Chemotherapy Patients



Fourteen million commercially insured lives; 104,473 cancer patients. Chemotherapy patients exclude patients on hormonal therapy only.

CLL indicates chronic lymphocytic leukemia; PPPM, per patient per month.
Source: Milliman Analysis of Medstat 2007; Milliman Health Cost Guidelines 2009.
Reprinted with permission from Fitch K, Pyenson B. *Cancer Patients Receiving Chemotherapy: Opportunities for Better Management*. Milliman; March 30, 2010.

Medicare population,[6] there was very little in the published literature to guide us in identifying where opportunities lie. We therefore entered into a partnership with Milliman to study costs of cancer care in the commercial population.[7]

The study analyzed data from Medstat 2007, a claims database of commercial insurers, including several BCBS plans, covering 28 million lives. We focused on the top 10 cancer diagnoses, which represented 70,000 individuals. Cancer was relatively uncommon in this cohort, only 0.7% of all covered individuals, but cancer claims made up almost 10% of the cost. The 10 cancer diagnoses represented about 65% of all cancer diagnoses in this cohort, with breast cancer being the most common diagnosis. Among the cancer patients, about 25% received chemotherapy in a given year. The average cost per cancer patient receiving chemotherapy was about $110,000 per year, 4 times as much as the average cancer patient not receiving chemotherapy. Further, the cost for cancer patients receiving chemotherapy was dramatically higher, more than 20-fold greater, than the cost for patients with other chronic diseases like diabetes.

So how is the money spent? The majority of the charges were for outpatient services (**Figure 2**). In analyzing the outpatient costs, only 25% of costs were for chemotherapy. The remainder of the costs included imaging, outpatient surgery, and other ambulatory services. We also found there were about 2 hospitalizations per year and 2 emergency department (ED) visits per year in chemotherapy-treated patients, half of which could be attributed to chemotherapy toxicity. Unfortunately, we found relatively low hospice utilization rates. And more concerning, we found a large cohort of patients who died in the hospital and received chemotherapy within 14 days of death.

As with the published experience with the Dartmouth Atlas, we identified marked regional variations in care (**Figure 3**). The range in chemotherapy costs was almost a third higher in the high-utilizing regions, and not surprisingly, hospital admits and ED visits varied 2-fold and 4-fold respectively from low- to high-utilizing regions. This data set identifies opportunities for cost control, especially in chemotherapy costs, hospital and ED costs, and end-of-life costs.

The US Oncology Network has, for the last 6 years, focused on the ability to control costs by adopting an evidence-based treatment platform, Level I Pathways. These evidence-based treatment guidelines are embedded in the iKnowMed EHR and offered as a decision support tool, with reports that allow implementation of a process improvement methodology. We have reported on the impact of these evidence-based pathways in our network in patients with lung cancer and colorectal cancer.

Our first study, in non-small cell lung cancer patients, was a collaboration with Aetna.[8] Over an 18-month period, we looked at cost of care in 1400 patients at 8 sites in the US Oncology Network. Clinical data including stage of disease and line of therapy were documented. We studied chemotherapy costs as well as costs associated with acute care visits, E and M codes, laboratory, and supportive care drugs. Within our sites of service, 1100 of 1400 patients were treated according to guidelines, considered "on pathway," and 300 of 1400 were treated "off pathway." There was a substantial cost difference between the groups, with a 35% reduction in chemotherapy costs associated with being treated on pathway ($18,000 vs $27,700). Importantly, survival of those treated on pathway was identical to those treated off pathway (**Figures 4A and 4B**).

We also analyzed the effect of pathways compliance in colon cancer.[9] In this second study, we looked at costs associated with pathway status (on or off) in a national database with the assistance of Milliman. Since survival data were not available in this claims system, we analyzed survival with respect to pathways status within iKnowMed. We again found a substantial savings associated with being "on pathway," about 35%. Interestingly, we found evidence that disease-free survival and overall survival with treatment on pathway were at least as good as in the off-pathway cohort. A preliminary review of inpatient charges and hospitalization rates within the on pathway/off pathway cohorts suggests reduced costs and utilization in the on-pathway group,

"There will need to be trust between payers and providers to succeed in this system. Ultimately, the reward will be improved value and enhanced quality."

—Michael Kolodziej, MD, and J. Russell Hoverman, MD, PhD
US Oncology

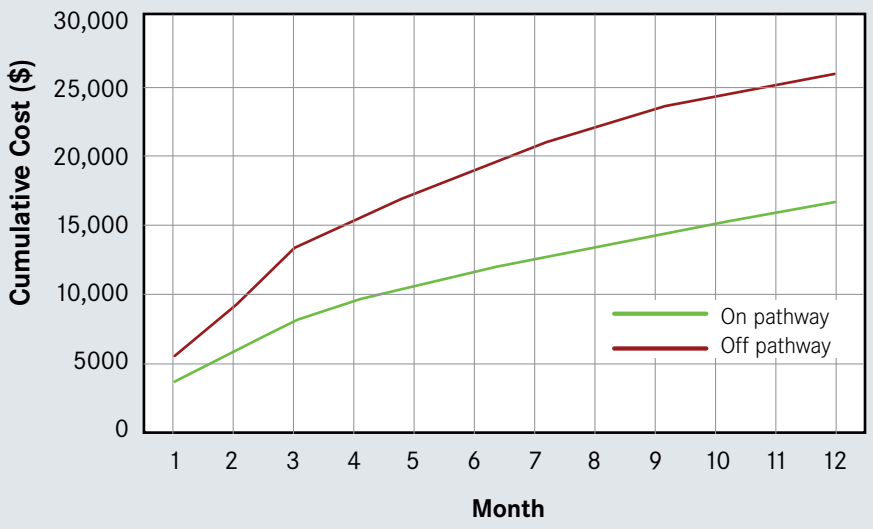
THE AMERICAN JOURNAL OF MANAGED CARE

Figure 3. Variation in Care for Patients

	Chemotherapy Related Inpatient Hospital Admits/1000	Chemotherapy-related ED Visits/1000	Average Chemotherapy Drug Costs per Chemotherapy Patient
National Average	378 (average cost per admit $22,000)	929 (average cost per ED visit $800)	$22,353
High Utilizing Region	484	1626	$27,494
Low Utilizing Region	223	465	$17,212

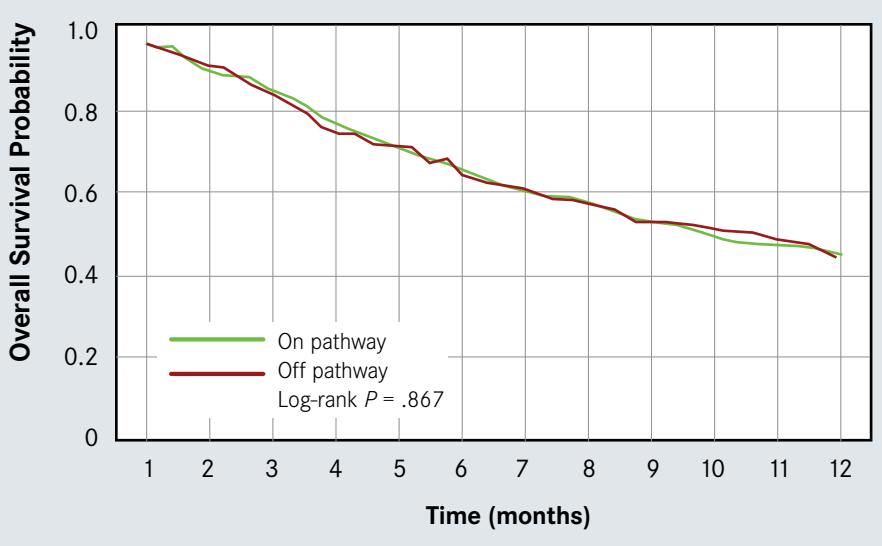
ED indicates emergency department.
Source: Milliman Analysis of Medstat 2007.
Reprinted with permission from Fitch K, Pyenson B. *Cancer Patients Receiving Chemotherapy: Opportunities for Better Management*. Milliman; March 30, 2010.

Figure 4A. 12-Month Cumulative Cost by Pathway Status



Reprinted with permission from Neubauer et al.[8]

Figure 4B. Overall Survival by Pathway Status



Overall Survival Probability

Pathway status	3 month	6 month	9 month	12 month
All patients (n = 1409)	0.82	0.64	0.53	0.46
On pathway (n = 1095	0.82	0.65	0.53	0.45
Off pathway (n = 314)	0.80	0.64	0.54	0.46

Reprinted with permission from Neubauer et al.[8]

providing further evidence of cost savings associated with adherence to these evidence-based treatment guidelines.

This body of data makes a compelling case for value associated with a disciplined, cost-conscious, evidence-based approach to chemotherapy decision making. This value derives from clearly reduced costs but also improved outcomes. The value associated with this approach is physician developed and driven. And a similar physician developed and driven approach may well be feasible to attack costs associated with hospitalizations and ED visits and especially end-of-life care, where there is ample opportunity for improvement.

There are clearly challenges to the broad adoption of this approach. First, there are innumerable evidence-based treatment guidelines. Most of these are at best cost neutral and at worst cost insensitive. It would be a mistake to assume an equal benefit across all of these guidelines. Second, this approach requires a genuine attempt at process improvement. Reporting and accountability are mandatory. Without physician buy-in, the process is doomed to failure. Finally, there is widespread dissatisfaction with the current oncology reimbursement methodology. A transition to a methodology that financially rewards high-level, quantifiable performance will greatly enhance likelihood of general acceptance. There will need to be trust between payers and providers to succeed in this system. Ultimately, the reward will be improved value and enhanced quality. **EBO**

Author Affiliations: From New York Oncology Hematology and Albany Cancer Center (MK), Albany NY; Texas Oncology (JRH), Austin, TX; and US Oncology (MK, JRH), Houston, TX.

Funding Source: None.

Author Disclosures: Drs Kolodziej and Hoverman report employment with US Oncology, Houston, TX.

Authorship Information: Concept and design (MK, JRH); acquisition of data (MK); analysis and interpretation of data (MK, JRH); drafting of the manuscript (MK, JRH); critical revision of the manuscript for important intellectual content (MK, JRH); provision of study materials or patients (MK); and supervision (MK).

References

1. Borger C, Smith S, Truffer C, et al. Health spending projections through 2015: changes on the horizon. *Health Aff (Millwood)*. 2006;25:w61-w73.

2. Tangka FK, Trogdon JG, Richardson LC, Howard D, Sabatino SA, Finkelstein EA. Cancer treatment cost in the United States: has the burden shifted over time? *Cancer*. 2010;116(14):3477-3484.

3. Congressional Budget Office. *Geographic Variation in Healthcare Spending 2005*. www.cbo.gov/ftpdocs/89xx/doc8972/2-15-GeogHealth.pdf.

4. The Trustees of Dartmouth College. *The Dartmouth Atlas of Health Care*. http://www.dartmouthatlas.org/.

5. Hoverman JR, Robertson SM. Lung cancer: a cost and outcome study based on physician practice patterns. *Dis Manag*. 2004;7:112-123.

6. Hassett MJ, Neville BA, Weeks JC. The relationship between cost, quality, and outcomes among women with breast cancer in SEER-Medicare. *J Clin Oncol*. 2011;29:384S(suppl; abstr 6001).

7. Kolodziej M, Hoverman JR, Garey JS, et al. Benchmarks for value in cancer care: an analysis of a large commercial population. *J Oncol Pract*. 2011;7(5):301-306.

8. Neubauer MA, Hoverman JR, Kolodziej M, et al. Cost-effectiveness of evidence-based treatment guidelines for the treatment of non-small-cell lung cancer in the community setting. *J Oncol Pract*. 2010;6(1):12-18.

9. Hoverman JR, Cartwright TH, Patt DA, et al. Pathways, outcomes, and costs in colon cancer: retrospective evaluations in two distinct databases. *J Oncol Pract*. 2011;7(3)(suppl 3):52s-59s.

Long-Term Breast Cancer Patient Follow-Up Care

Money Well Spent?

Anna Azvolinsky, PhD

The 29th Annual Miami Breast Cancer Conference culminated in a thought-stirring last session. J. Michael Dixon, MBChB, MD, professor of surgery at the University of Edinburgh and clinical director of the Edinburgh Breast Unit at the Western General Hospital, Edinburgh, Scotland, and Patrick I. Borgen, MD, director of the Brooklyn Breast Cancer Program at Maimonides Breast Cancer Center in Brooklyn, New York, debated the pros and cons of long-term clinical follow-up care of patients with breast cancer.

The Con Argument: Clinical Exams Increase Costs and Psychological Distress

"It is always difficult to give up something that you are used to doing," began Dixon's argument against frequent follow-up for breast cancer patients in remission. "There are numerous guidelines but very little guidance," he said, highlighting the disparity in follow-up guidance in different parts of the world. Currently, North American guidelines suggest that clinical examinations take place every 3 to 6 months for the first 3 years, every 6 to 12 months for the next


J. Michael Dixon, MBChB, MD

4 to 5 years, and on an annual basis thereafter for women in remission from breast cancer.

Dixon challenged the notion that intense follow-ups improve outcomes for women previously treated for breast cancer. He highlighted studies that have looked at the detection of systemic recurrence in women previously diagnosed and treated for breast cancer.

A 1994 randomized study comparing patients undergoing intensive laboratory and x-ray–based follow-up assessments to standard of care found more metastases earlier in the intensely followed group—but at the expense of significant false-positive rates.[1] Dixon concluded that because the 5- and 10-year data analysis did not show any differences in overall survival in the 2 trial arms, the intense follow-up was not cost-effective.

A 1999 study compared the 10-year mortality rates in women who had undergone treatment for primary breast cancer. The women had either intense or standard clinical follow-up.[2] The more intense protocol did not offer a survival advantage, the study concluded.

A more recent analysis from 2007 showed that traditional routine clinical checkups were not sufficient enough to prevent disease recurrence, questioning the need for frequent follow-ups.[3] The study authors stated that alternative follow-up methods were acceptable for patients, as these did not decrease either quality of life or anxiety about recurrence. Less-frequent visits can, however, offer significantly lower costs and time savings.

"Just because you can, doesn't mean you should," Dixon stressed, pointing out that recurrent clinical follow-ups resulted not only in unnecessarily increased healthcare costs, but also in creating psychological distress that can negatively affect the health of a patient.

Dixon's solution? More effective ways of achieving improved patient outcomes with minimal psychological stress by seeing regular physiotherapists or nurses, rather than undergoing regular clinical follow-up assessments.

Dixon discussed a recent United Kingdom study that followed a total of 32,877 women from the West Midlands Cancer Intelligence Unit Cancer registry; 18,706 of the included women had breast conservation surgery, and 15,171 had mastectomies following a breast cancer diagnosis. Analyses showed that earlier detection generally led to better outcomes. The study also showed that clinically detected recurrences did worse compared with detection via mammography or by the patient herself. Overall survival was very much dependent on the size of the second tumor detected. The aim should be to detect recurrence as early as possible, Dixon concluded.

How much does follow-up cost? Dixon discussed an economic model, in British pounds, that incorporated different treatment regimens, the estimated likely survival benefit per regimen, and the cost per incremental quality-adjusted life-years (QALYs), among other metrics, for a woman aged 57 years. The utilization of extra tests such as mammography, clinical examination, and magnetic resonance imaging (MRI) did not lead to added benefit, except for younger women. The top 3 most cost-effective options were mammography, followed by clinical examination and mammography, and clinical examination and an MRI.

"Current clinical follow-up programs waste time and resources," Dixon said. They are much better off targeting specific groups that have clinical issues, he concluded. "Local recurrence rates are falling. Therefore, the cost detection of each recurrence is increasing."

The Pro Argument: Patient Care Is Personal

Borgen's pro argument emphasized the soft side of the physician-patient relationship and the fundamental goal of patient follow-up—peace of mind and regular surveillance to catch recurrence as early as possible. Borgen believes that there is a survival benefit of patients seeing their oncologist regularly.

Borgen stated that he was surprised at the seemingly high rate of clinically detected first recurrences, 13.5%, cited by Dixon. "My guess is that the rate is actually far lower than this," he commented.

Borgen discussed the subjective perspective of the relationship between the physician and the cancer patient, emphasizing the relationship of the patient with the surgeon as the first point of contact and a help in "navigating the maze of diagnostic and treatment options." Borgen said he believes that patients often are reassured by staying in close contact with their surgeon as a "source of information."

From a physician's perspective, the benefit of following a breast cancer patient in the long term is training. Long-term follow-up can be highly valuable for residents and physicians early in their careers. Understanding the long-term effects of surgery and therapy help better train surgeons and oncologists, argued Borgen.

Borgen concluded with something that hits home for most clinicians (and patients): the personal aspect of care. "It's always problematic to apply national, aggregate numbers to the patient that is sitting in front of you," he said. "The only way to really achieve what Dr Dixon discussed is a policy change in the [United States]. That policy change would likely be driven by insurance payers who would simply refuse to pay for follow-up care."

Is this the future in the United States? Not without relevant, convincing, large-scale patient follow-up data. **EBO**


Patrick I. Borgen, MD

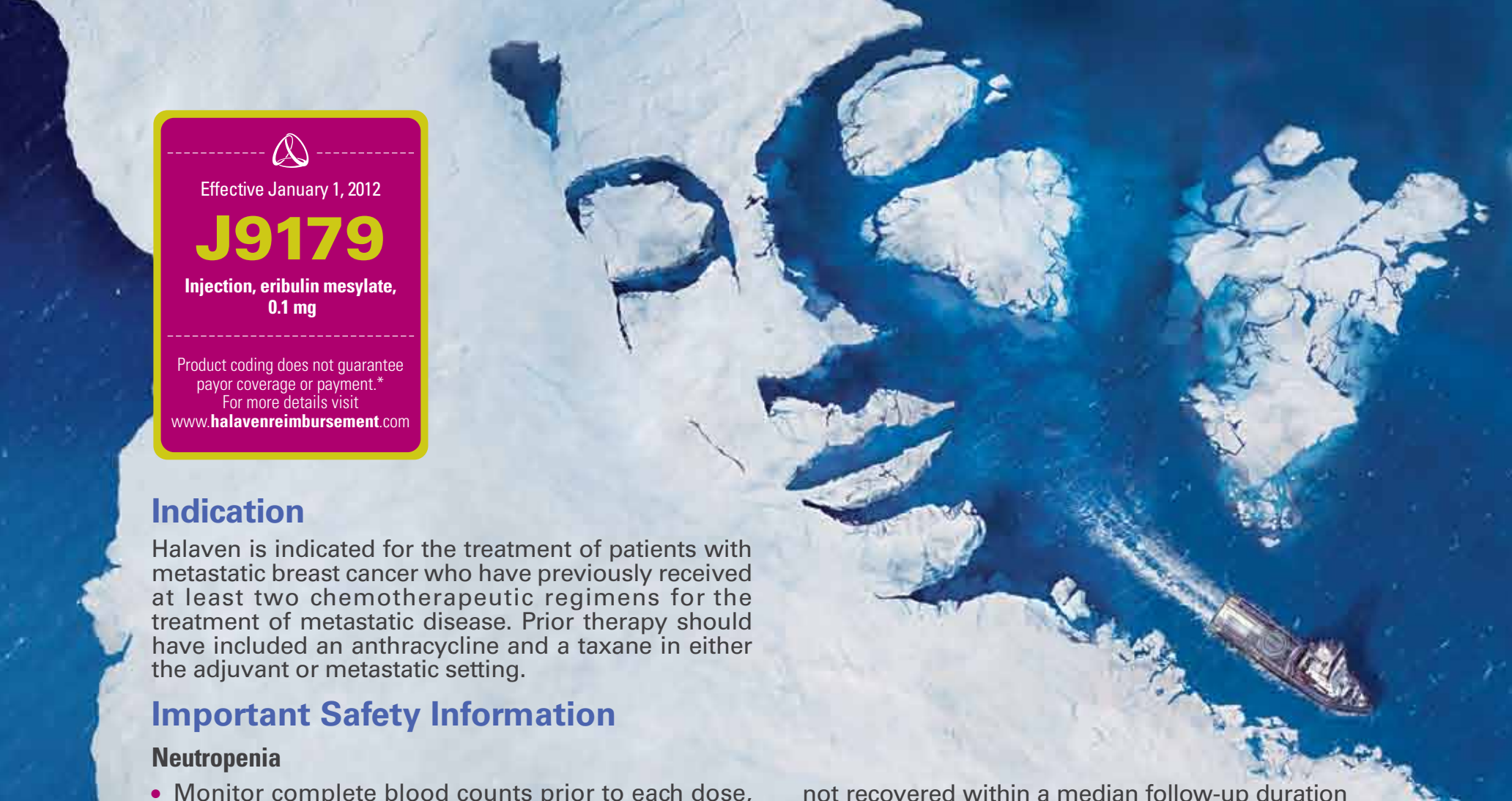
Funding Source: None.
Author Disclosure: The author reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.
Authorship Information: Concept and design; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

References

1. Del Turco MR, Palli D, Cariddi A, Ciatto S, Pacini P, Distante V. Intensive diagnostic follow-up after treatment of primary breast cancer: a randomized trial. *JAMA*. 1994;271(20):1593-1597.

2. Palli D, Russo A, Saieva C, et al. Letter to the editor. Intensive vs clinical follow-up after treatment of primary breast cancer: 10-year update of a randomized trial. *JAMA*. 1999;281(17):1586.

3. Montgomery DA, Krupa K, Cooke TG. Alternative methods of follow up in breast cancer: a systematic review of the literature. *Br J Cancer*. 2007;96:1625-1632.



Effective January 1, 2012

J9179

Injection, eribulin mesylate, 0.1 mg

Product coding does not guarantee payor coverage or payment.*
For more details visit
www.**halavenreimbursement**.com

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)

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; 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

Please see accompanying brief summary of Halaven full Prescribing Information.

References: 1. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology™: Breast Cancer.* Version 2.2011. http:NCCN.org. Published January 5, 2011. Accessed October 18, 2011.† **2.** Halaven [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2010. **3.** Saad ED, Katz A, Buyse M. Overall survival and post-progression survival in advanced breast cancer: a review of recent randomized clinical trials. *J Clin Oncol.* 2010;28(11):1958-1962. **4.** Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med.* 2001;344(11):783-792. **5.** Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med.* 2006;355(26):2733-2743. **6.** von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2–positive advanced breast cancer: a German Breast Group 26/Breast International Group 03-05 study. *J Clin Oncol.* 2009;27(12):1999-2006. **7.** Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med.* 2007;357(26):2666-2676. **8.** Robert NJ, Dieras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC). *J Clin Oncol.* 2009;27(suppl; abstr 1005). **9.** Sparano JA, Vrdoljak E, Rixe O, et al. Randomized phase III trial of ixabepilone plus capecitabine versus capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol.* 2010;28(20):3256-3263. **10.** Jones SE, Erban J, Overmoyer B, et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol.* 2005;23(24):5542-5551. **11.** Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet.* 2011;377(9769):914-923.

*Eisai cannot guarantee payment of any claim. Coding, coverage, and reimbursement may vary significantly by payor, plan, patient, and setting of care. Actual coverage and reimbursement decisions are made by individual payors following the receipt of claims. For additional information, customers should consult with their payors for all relevant coding, reimbursement, and coverage requirements. It is the sole responsibility of the provider to select the proper code and ensure the accuracy of all claims used in seeking reimbursement. All services must be medically appropriate and properly supported in the patient medical record.

Scan this code to visit
www.halaven.com

A preferred single agent in the **NCCN Guidelines™**[1]

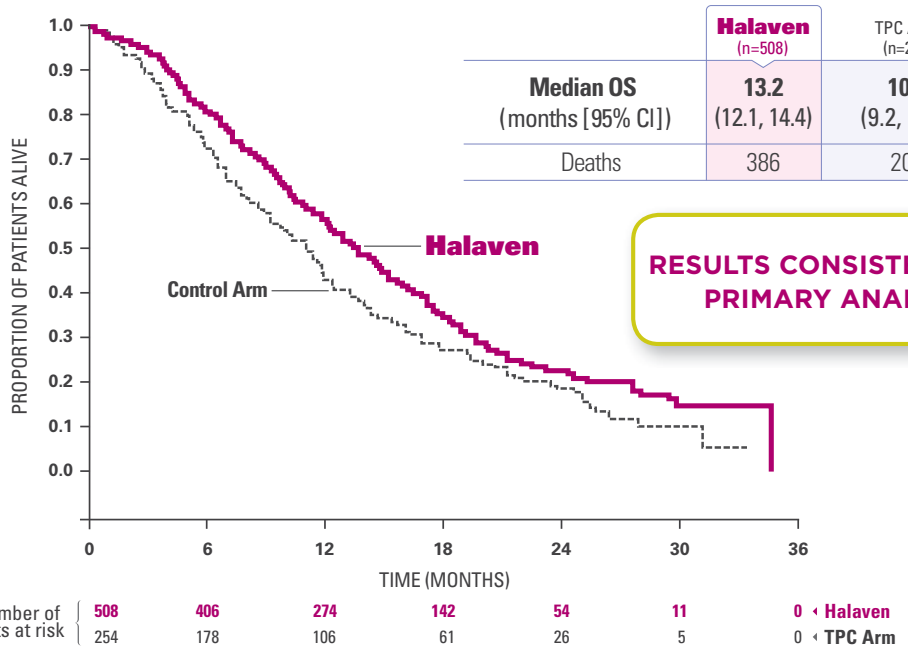
DISCOVER OVERALL SURVIVAL

Halaven®: The FIRST and ONLY third-line, single-agent therapy proven to significantly extend overall survival in patients with metastatic breast cancer (MBC)[2-10]

The Phase III EMBRACE* trial met its primary endpoint of overall survival (OS)[2,11]

- In the primary analysis, conducted when ~50% of events (deaths) had been observed, median OS with Halaven vs Control Arm (**T**reatment of **P**hysician's **C**hoice [TPC]) was 13.1 months (95% CI: 11.8, 14.3) vs 10.6 months (95% CI: 9.3, 12.5), HR=0.81 (95% CI: 0.66, 0.99) (*P*=0.041)†[2,11]

UPDATED OVERALL SURVIVAL ANALYSIS (UNPLANNED)†[2]



	Halaven (n=508)	TPC Arm (n=254)
Median OS (months [95% CI])	**13.2** (12.1, 14.4)	**10.6** (9.2, 12.0)
Deaths	386	203

RESULTS CONSISTENT WITH PRIMARY ANALYSIS[2]

Results from an updated, unplanned survival analysis of the Phase III, open-label, multicenter, multinational EMBRACE trial of Halaven vs TPC in patients with MBC (N=762). The primary endpoint was OS. Patients were randomized (2:1) to receive either Halaven 1.4 mg/m^2 IV 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.[2,11]

CI=confidence interval; HR=hazard ratio.
*EMBRACE=**E**isai **M**etastatic **Br**east Cancer Study **A**ssessing Physician's **C**hoice vs **E**7389 (Eribulin).
†Conducted in the intent-to-treat (ITT) population.

Halaven: Quick administration

- 2- to 5-minute intravenous infusion on Days 1 and 8 of a 21-day cycle[2]

Halaven: Safety profile

- Studied in the Phase III EMBRACE trial[2]

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%)
- Peripheral neuropathy (5%) was the most common adverse reaction resulting in discontinuation

THE EISAI ASSISTANCE PROGRAM | 1.866.613.4724

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

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

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

THE AMERICAN JOURNAL OF MANAGED CARE

Disease Overview SP131

Myeloproliferative Disorders and Myelofibrosis

Marjorie P. Zimmerman, MS, BSPharm, RPh; and Stanton R. Mehr

Myeloproliferative disorders are associated with bone marrow malfunction. The bone marrow contains stem cells that develop into red blood cells, white blood cells, and platelets in appropriate proportion. A change in the DNA of a single stem cell causes a growth advantage for one of the cell types, which leads to an abnormal under- or over-production of the respective cell types.[1]

Polycythemia vera, essential thrombocythemia, and primary myelofibrosis together comprise the myeloproliferative neoplasms, which are considered Philadelphia-chromosome–negative chronic myeloproliferative neoplasms.[1-4]

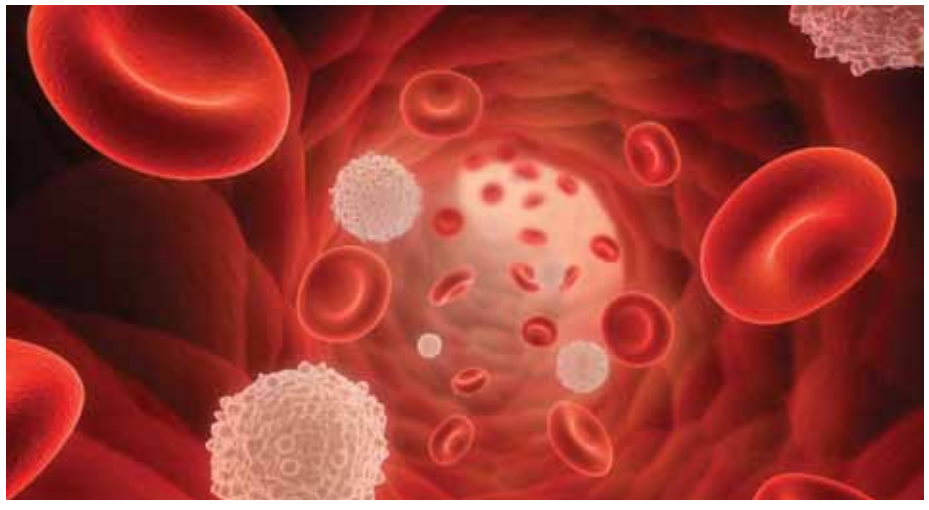
Polycythemia vera is characterized by an excessive amount of red blood cells being formed by the bone marrow. There may also be an increased number of leukocytes (white blood cells) and platelets and an enlarged spleen. Essential thrombocythemia is the result of the overproduction of platelets. As either of these 2 disorders progresses, bone marrow scarring may occur, which leads to myelofibrosis. Polycythemia vera progresses to myelofibrosis in about 15% of the cases, while only a small number of patients with essential thrombocythemia progress to myelofibrosis.[3] Myelofibrosis can also arise without pre-existing conditions. Primary myelofibrosis and myelofibrosis secondary to polycythemia vera and essential thrombocythemia have a common mutant allele—*JAK2*.[5] About 50% of patients with essential thrombocythemia have this same gene mutation as well as 95% of patients with polycythemia vera.[3]

Each of these diseases typically occurs in the fifth or sixth decade of life. Patients with essential thrombocythemia can lead a normal life with an unaffected life expectancy. The median survival for polycythemia vera is more than 10 years with treatment. Myelofibrosis has the worst prognosis of the 3 diseases, as it has a median survival of less than 3 years but younger patients (<55 years) have survivals of more than 10 years.[5] Patients are stratified by risk (low risk, intermediate-1, intermediate-2, or high risk) based on patients' number of risk factors, which is predictive for survival.[2,6] Approximately 10% to 20% of patients with myelofibrosis progress to acute myelogenous leukemia.[7]

Treatment is guided by addressing the presenting risk factors, with the goal of extending survival.[2] Based on few effective treatments (and the relative rarity of these cancers), evidence for the economic value of treatment has not yet been quantified.

Polycythemia, essential thrombocythemia, and myelofibrosis are classified as orphan diseases, as they affect fewer than 200,000 people in the United States at any given time. Currently, these diseases are not measured by the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Market research has estimated that all 3 diseases have an annual incidence of fewer than 3 patients per 100,000 population.[3,4,8] In 2003, the prevalence of polycythemia vera was 22 per 100,000 (65,243 patients total), and the prevalence of essential thrombocythemia was 24 per 100,000 (71,078 patients).[9] Researchers investigating myelofibrosis in 1999 reported an incidence of 1.46 per 100,000, with a total prevalence of 30,000 patients.[10]

It is therefore understandable that for most health plans, these myeloproliferative neoplasms do not merit intense scrutiny. However, the available treatments for these disorders vary quite dramatically, and the therapeutic options for myelofibrosis in particular have changed dramatically in the past year.



Sebastian Kaulitzki (iStock)

Current Treatment Options

Patients without symptoms or with minimal symptoms are usually managed with a watch-and-wait strategy, until the patient's risk score worsens or hematological abnormalities necessitate intervention.[2]

Therapies for polycythemia vera and essential thrombocythemia are similar, including phlebotomy to reduce the number of circulating red blood cells, low-dose aspirin to reduce the chance for blood clots (and to alleviate vasomotor symptoms experienced by some patients), hydroxyurea and anagrelide for those at high risk for blood clots, and interferon. Hydroxyurea is also used to treat splenomegaly, a complication of these disorders.[4,11,12]

Until late 2011, there were no approved therapies for myelofibrosis. Off-label therapies employed included hydroxyurea, androgens, corticosteroids, erythropoiesis-stimulating agents, danazol, thalidomide, lenalidomide, busulfan, melphalan, cladribine, and interferon. Blood transfusions, radiation, and removal of the spleen have been tried as well. However, these therapies have not prolonged survival.[7] The only known cure for myelofibrosis has been allogeneic hemopoietic stem-cell transplantation, which is itself associated with high morbidity and mortality as well as high costs.[2,7,13]

Ruxolitinib (Jakafi), an oral *JAK1* and *JAK2* kinase inhibitor, was approved in November 2011 for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post–polycythemia vera myelofibrosis, and post–essential thrombocythemia myelofibrosis.[14] Two phase III trials demonstrated significant improvement compared with best available therapy for spleen size, symptoms, and burden reduction, as well as for quality of life.[14-16] However, the reduced spleen size was not shown to be consistently durable in a phase I/II study and neither phase III study reported a significant survival benefit.[17,18] This agent is commonly associated with hematologic side effects; anemia was reported in 96% of patients taking ruxolitinib (grade 3/4, 45%), and thrombocytopenia was reported in 70% (grade 3/4, 13%).[14] This first *JAK* inhibitor therapy for myelofibrosis has been long anticipated; yet, the value of this treatment is not truly known. The treatment of adverse events and its overall effect in avoidance of other therapies will need to be included in the value equation. It is likely that it will be covered by health plans because of the low incidence of the disorder and the lack of other effective treatments.

Economics

Until recently, very little information was available about the costs of myeloproliferative neoplasms. A study presented at the American Society of Hematology meeting in December 2011 showed that annual medical and drug costs for patients with myelofibrosis neoplasms were 2 to 6 times that of patients with ailments other

Highlights From the 16th Annual International Congress on Hematologic Malignancies

PER PHYSICIANS' EDUCATION RESOURCE, LLC

David P. Steensma, MD, attending physician, hematologic oncology, Dana-Farber Cancer Institute, discusses iron chelation therapy for myeloproliferative disorders (http://hcp.lv/KmidSu)

Ruben A. Mesa, MD, Professor of Medicine, Chair, Division of Hematology & Medical Oncology, Mayo Clinic, explains the role of JAK2 inhibitors in the treatment of myelofibrosis (http://hcp.lv/JvFiQu)

THE AMERICAN JOURNAL OF MANAGED CARE

than cancer.[19] This study tracked the costs of 25,145 patients with these disorders, based on claims from a database of about 100 payers across the country.

For patients with myelofibrosis, mean total annual costs were $34,690, with outpatient costs accounting for 53% of the total (mean, $18,395). Inpatient visits (23%, $8106), drug costs (22%, $7803), and emergency department visits (1%, $386) accounted for the remaining costs. Patients with myelofibrosis incurred the greatest costs, followed by patients with essential thrombocythemia (mean annual total, $19,672) and polycythemia vera (mean annual total, $11,927).[19]

Drivers of Cost

Drugs, laboratory costs, phlebotomy, radiation, surgery (including splenectomy), and allogeneic hemopoietic stem-cell transplantation all contribute to the costs of treating and managing myeloproliferative disorders. It is likely that the approval of ruxolitinib will have a significant effect on the proportion of total costs associated with pharmaceutical treatment (depending on its coverage by payers and anticipated utilization). Like some other oral oncology treatments, ruxolitinib is intended to be taken chronically, as long as spleen size is reduced and symptoms are improved. All the therapies except for allogeneic hemopoietic stem-cell transplantation are palliative in nature, with no impact on overall survival.

It remains to be seen whether *JAK* inhibitors in development can cure the disease. However, drug therapies that reduce the burden of the disease have the potential to reduce the costs currently associated with managing the disease, principally by delaying the need for the most costly treatments, like allogeneic hemopoietic stem-cell transplantation. **EBO**

Funding Source: None.

Author Disclosures: Mr Mehr reports receiving payment for involvement in the preparation of this article. Ms Zimmerman reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (MPZ); acquisition of data (SRM, MPZ); analysis and interpretation of data (SRM, MPZ); drafting of the manuscript (SRM, MPZ); critical revision of the manuscript for important intellectual content (SRM, MPZ); and sidebar development (SRM).

References

1. Myeloproliferative Disorders Research Consortium. What are myeloproliferative disorders. http://www.mpd-rc.org/readarticle.php?article_id=1. Published September 8, 2006. Accessed January 4, 2012.

2. Vannucchi AM. Management of myelofibrosis. *Hematology Am Soc Hematol Educ Program*. 2011;2011:222-230.

3. Myeloproliferative neoplasms (MPNs) Research Foundation. Primary myelofibrosis. http://www.mpnresearchfoundation.org/Primary-Myelofibrosis. Accessed January 4, 2012.

4. Advani A, Theil K. Chronic myeloproliferative disorders. Cleveland Clinic Center for Continuing Education website. http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/hematology-oncology/chronic-myeloproliferative-disorders/. Accessed January 3, 2012.

5. Tefferi A, Barosi G, Mesa RA, et al. International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia. *Blood*. 2006;108(5):1497-1503.

6. Tefferi A. Primary myelofibrosis: 2012 update on diagnosis, risk stratification, and management. *Am J Hematol*. 2011:86(12):1017-1026.

7. Cervantes F, Pereira A. Prognosticating in primary myelofibrosis [published online ahead of print November 10, 2011]. *Curr Hematol Malig Rep*.

8. JAK inhibitor provides rapid, durable relief for myelofibrosis patients. NCCN.com. http://www.nccn.com/component/content/article/76-member-institution-spotlight/318-jak-inhibitor-provides-rapid-durable-relief-for-myelofibrosis-patients.html. Published September 15, 2010. Accessed January 5, 2012.

9. Ma X, Vanasse G, Cartmel B, et al. Prevalence of polycythemia vera and essential thrombocythemia. *Am J Hematol*. 2008;83(5):359-362.

10. Mesa RA, Silverstein MN, Jacobson SJ, Wollan PC, Tefferi A. Population-based incidence and survival figures in essential thrombocythemia and agnogenic myeloid metaplasia: an Olmsted county study, 1976-1995. *Am J Hematol*. 1999;61(1):10-15.

11. Tefferi A, Spivak JL. Polycythemia vera: scientific advances and current practice. *Semin Hematol*. 2005;42(4):206-220.

12. Tefferi A, Solberg LA, Silverstein MN. A clinical update on polycythemia vera and essential thrombocythema. *Am J Med*. 2000;109(2):141-149.

13. Barbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol*. 2011;29(6):761-770.

14. Jakafi package insert. Incyte Pharmaceuticals; November 2011. http://www.incyte.com/products/uspi_jakafi.pdf. Accessed January 4, 2012.

15. Harrison CN, Kiladijan JJ, Al-Ali HK, et al. Results of a randomized study of the JAK inhibitor INC424 compared with best available therapy (BAT) in primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PETMF) (abstract). *J Clin Oncol*. 2011;29:LBA6501A.

16. Verstovsek S, Mes R, Gotlib JR, et al. Results of COMFORT-I, a randomized double-blind phase III trial of JAK 1/2 inhibitor INCB18424 (424) versus placebo (PB) for patients with myelofibrosis (MF) (abstract). *J Clin Oncol*. 2011;29:6500.

17. Tefferi A, Litzow MR, Pardanani A. Long-term outcome of treatment with ruxolitinib in myelofibrosis. *N Engl J Med*. 2011;365(15):1455-1457.

18. JAK inhibitor ruxolitinib demonstrates significant clinical benefit in myelofibrosis. ASCO Daily News. http://chicago2011.asco.org/ascodailynews/comfort.aspx. Published June 2011. Accessed January 6, 2012.

19. Price GL, Pohl GM, Xie J, et al. A retrospective observational study of annual healthcare costs for patients with forms of myeloproliferative neoplasms (MPN). ASCO abstract 2060. December 10, 2011.

Additional Suggested Reading

Tefferi A, Lasho TL, Jimma T, et al. One thousand patients with primary myelofibrosis: the Mayo Clinic experience. *Mayo Clin Proc*. 2012;87(1):25-33.
A description of the experience of the Mayo Clinic's 1000 consecutive patients with primary myelofibrosis, from 1977 to the present.

Kundranda MN, Tibes R, Mesa RA. Transformation of a chronic myeloproliferative neoplasm to acute myelogenous leukemia: does anything work [published online ahead of print December 15, 2011]? *Curr Hematol Malig Rep*.
Over the natural course of Bcr/Abl-negative myeloproliferative neoplasms of essential thrombocythemia, polycythemia vera, and primary myelofibrosis, transformation to acute myelogenous leukemia is more likely; although a rare event, the molecular events leading to transformation are poorly defined. The authors describe the latest advances in our understanding of the biology of leukemic transformation and current clinical therapies that are available for this patient population.

Vakil E, Tefferi A. BCR-ABL1–negative myeloproliferative neoplasms: a review of molecular biology, diagnosis, and treatment. *Clin Lymphoma Myeloma Leuk*. 2011;11(suppl 1):S37-S45.
The mutation JAK2V617F is the best characterized of the BCR-ABL1-negative neoplasm mutations, with an estimated prevalence of more than half of patients with primary myelofibrosis, according to researchers from Ireland. Current diagnostic strategies rely on molecular markers, and their prognostic value continues to be investigated. There have been promising results from clinical trials that involve the JAK tyrosine kinase inhibitors TG101384 and INCB018424, but their role in future therapy is yet to be established.

Santos FP, Verstovsek S. JAK2 inhibitors: are they the solution? *Clin Lymphoma Myeloma Leuk*. 2011;11(suppl 1):S28-S36.
The discovery of the JAK2V617F mutation in patients with Philadelphia chromosome–negative myeloproliferative neoplasms started the era of targeted therapy for these diseases. The authors review recent data on JAK2 inhibitors for the management of patients with Philadelphia chromosome–negative myeloproliferative neoplasms.

Passamonti F. Prognostic factors and models in polycythemia vera, essential thrombocythemia, and primary myelofibrosis. *Clin Lymphoma Myeloma Leuk*. 2011;11(suppl 1):S25-S27.
Prognosis in primary myelofibrosis is predicted at diagnosis by a combination of different risk factors, such as advanced age (>60 years), anemia, leukocytosis (white blood cell count >25 x 10^9/L), the presence of blast cells (≥1%), and the presence of constitutional symptoms. This model may also predict survival when applied during follow-up.

Stein BL, Crispino JD, Moliterno AR. Janus kinase inhibitors: an update on the progress and promise of targeted therapy in the myeloproliferative neoplasms. *Curr Opin Oncol*. 2011;23(6):609-616.
The discovery of the JAK2 V617F mutation in the classical myeloproliferative neoplasms has ushered in a new era of scientific discovery in these diseases, resulting in a molecular classification and an improved understanding of disease pathogenesis. The initial enthusiasm for these agents has been tempered by recognition that JAK2 V617F may represent only 1 component of lesions driving the heterogeneity of the MPN. It might be rational to give these inhibitors along with other agents that target alternate mechanisms of the disease pathogenesis.

Myeloproliferative Disorders Research Consortium. Chronic idiopathic myelofibrosis. http://www.mpd-rc.org/readarticle.php?article_id=4. Published September 6, 2006. Accessed January 4, 2012.
A fact sheet on myelofibrosis from an international consortium of nearly 40 institutions.

Ostojic A, Vrhovac R, Verstovsek S. Ruxolitinib: a new JAK1/2 inhibitor that offers promising options for treatment of myelofibrosis. *Future Oncol*. 2011;7(9):1035-1043.
A review of the clinical trial benefits of ruxolitinib.

Payer Perspective

Interview with Neil Minkoff, MD

***EBO*: How do you define value in patients being treated for myelofibrosis?**
Dr Minkoff: In general, value here is related to the difficulties with available chronic therapy. These patients will require transfusions and many get chemotherapy. A significant number get a marrow transplant. A significant number of patients will require splenectomy. Average survival is 5 years as the disease progresses. So, value will be defined in a number of ways: increased survival, reduction in transfusion, reduction in the need for splenectomy, or slowed progression of the disease.

***EBO*: In rare diseases like myelofibrosis, how does the value equation change compared with more common cancers, such as chronic myelogenous leukemia?**
Dr Minkoff: I don't think it does. The budget impact is different and the impact on trend is different, but a good evaluation of value should be the same for any product.

***EBO*: From the health plan perspective, what is the top objective when managing a patient with myelofibrosis: preventing/delaying transformation to acute myelogeneous leukemia? Avoiding the need for allogeneic stem cell transplants?**
Dr Minkoff: In myelofibrosis, we are still at a stage where any clinical improvement or delay in disease progression will lead to value. I don't limit my concern in a disease state like this to a single outcome.

***EBO*: How are payers like you managing the utilization of the targeted JAK-inhibitor drug ruxolitinib for these diseases?**
Dr Minkoff: As in many orphan conditions, management of new treatments is difficult. In this case, the drug is limited to patients with moderate-to-severe myelofibrosis and is often distributed through the specialty pharmaceutical channel in an effort to manage costs.

***EBO*: Are patients with myelofibrosis typically managed through case or care management in your plan?**
Dr Minkoff: They will have care managers to make sure their care is integrated. The care managers will also ensure that all follow-up appointments are booked, and that the patient is stable between visits. However, the actual management of the disease (stem-cell transplant, chemotherapy, etc) is generally done by the hematologist.

***EBO*: Do you emphasize the use of clinical practice guidelines or care pathways to ensure value in the treatment of rare cancers like myelofibrosis?**
Dr Minkoff: In general, the answer is no. For disease states like myelofibrosis, we depend more on the clinical acumen of the hematologists in the network.

Dr Minkoff is the founder of FountainHead HealthCare and former medical director, Harvard Pilgrim Health Plan, Wellesley, MA.

SABCS Conference Coverage

BRCA1/2 Genetic Testing Found Cost-Effective in Current Era

By Alice Goodman

Using current treatment costs and medical guidelines, genetic testing for *BRCA1/2* mutations among apparently healthy women at high risk of breast and/or ovarian cancer was deemed cost-effective in a study reported at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium in Texas.

From a societal perspective, the incremental cost-effectiveness ratio (ICER) increased from $9000 per quality-adjusted life-year (QALY) in a previous study [Holland MA et al. *Value Health*. 2009;12(2):207-216] to $30,600 per QALY. From a private payer perspective, the ICER is $36,800 per QALY.

A family history of breast and/or ovarian cancer increases the likelihood of being a *BRCA1/2* carrier, as well as the risk of developing breast and/or ovarian cancer. The 2009 study found *BRCA1/2* genetic testing to be a cost-effective strategy, regardless of the probability of a mutation. Since that study was published, medical guidelines for *BRCA* carriers have been updated to include annual use of magnetic resonance imaging (MRI) in women found to be *BRCA1/2*-positive.

The present study was conducted to determine if genetic testing for *BRCA* mutations remained a cost-effective strategy for high-risk women, given the additional guideline to include magnetic resonance imaging (MRI) for women who are identified as carriers, as well as updates in healthcare practice, policy, and the clinical specificity of testing over the past 10 years.

A semi-Markov decision model incorporated the annual use of MRI for screening in *BRCA* carriers, as well as updated treatment costs for breast and ovarian cancer from 2009 to 2011. The target population was asymptomatic women in the United States aged ≥35 years who were at elevated risk of carrying a *BRCA1/2* mutation. The base-case cost-utility analysis compared *BRCA1/2* testing followed by possible surgery when a mutation was identified versus no *BRCA1/2* testing or subsequent surgeries.

A sensitivity analysis confirmed that the model was robust to variation in the model parameters. Testing was preferred if the probability of carrying a mutation was greater than 3.1%. If the cost of genetic testing was above $8948, it would no longer be considered cost-effective, but the current upper boundary of cost estimates is $4500.

"The cost of the actual genetic test is not a barrier to its cost-effectiveness," said lead author Qinghua Li, MD, University of Rochester, New York. "Genetic testing for *BRCA1/2* mutations proved to be cost-effective for unaffected women whose pre-test mutation probability was 3.1% or higher based on family history," Li said.

From a societal perspective, the actual cost of testing versus no testing differed by $9844. From a private payer perspective, the actual cost of testing versus no testing was $11,868. These differences were used to compute ICERs and QALYs.

The study had several limitations, including sparse published data for several model parameters, such as the mortality reduction that can be attributed to MRI, the magnitude of cost reduction in earlier detection of breast cancer by MRI, and assuming 100% utilization of MRI by *BRCA*-positive women. "All women [who are *BRCA*-positive] will probably not have a breast MRI, and this may result in overestimating the cost of genetic testing," Li said. **EBO**

Funding Source: None.
Author Disclosure: The author reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.
Authorship Information: Concept and design; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

Skip ODonnell (iStock)

THE AMERICAN JOURNAL OF MANAGED CARE

Trends in the *2012 Eisai Oncology Digest*: Patient Demographics and Cancer Treatment Goals

This article was sponsored by Eisai Inc. The *2012 Eisai Oncology Digest* was commissioned and funded by Eisai Inc.

Introduction

Managing patients with cancer is extremely complex. Each patient with cancer is unique, and treatment options will vary depending on the type and stage of cancer and individual patient characteristics. Moreover, physicians and patients have preferences for certain tests and treatments; such preferences may be in conflict with the services covered by patients' health insurance providers. To help healthcare professionals understand some of this complexity, Eisai Inc sponsored an online national survey that asked patients with cancer about their experiences. Complete results from this survey were recently published in the *2012 Eisai Oncology Digest*.[1] This is the first article in a 3-part series that highlights findings from the survey; it describes the patient survey population and their overall perceptions of treatment and its goals.

Survey Participants

A total of 418 adult patients treated or recently treated (within past 5 years) for cancer participated in the survey. All patients were aware of their health insurance/drug coverage status and were currently receiving treatment with prescription medications (for any condition). More women participated in the survey than men (**Table 1**). Of the 418 patients, approximately one-third were between the ages of 21 and 54, one-third were between the ages of 55 and 64, and one-third were between the ages of 65 and 84. At the time of the survey, 237 participants (64%) were cancer free, while 151 (36%) had cancer.

The stage of cancer was implied based on whether the cancer was localized (confined to primary cancer site), regional (spread to regional lymph nodes), or distant (ie, metastasized). In the majority (69%) of patients surveyed, the cancer was localized, but the stage at diagnosis varied among cancer types (ie, 85% of prostate cancer was localized whereas 54% of colon/rectal cancer was regional/distant) (Table 1). The most common cancer types in this survey population were similar to those reported by the National Cancer Institute.[2]

Testing and Screening for Cancer

Prior to cancer diagnosis, most patients (as appropriate) received a mammogram (89%), Papanicolaou (Pap) test (89%), or prostate-specific antigen (PSA) test (85%) (**Table 2**). The lowest rates of screening related to testing for cervical human papillomavirus (HPV) (28%) and sigmoidoscopy (21%). Overall, the rates for testing/screening "prior to diagnosis" were significantly higher than those "since diagnosis" excepting oral cancer screenings, PSA blood tests, and skin checks. Results were similar in the subset of patients (n = 267) who were currently cancer free, suggesting an opportunity for improvement in screenings post diagnosis as part of a surveillance plan for cancer recurrence.

It should be noted that some of the screenings/tests were dependent on age. For example, colorectal and breast cancer screenings/tests were more prevalent in the older age groups, whereas HPV testing was more prevalent in the younger age groups. These age-related trends coincide with the testing and screening recommendations of the American Cancer Society (ACS) to: (1) perform mammograms annually beginning at age 40; (2) begin testing for colorectal cancer at age 50; and (3) begin screening for cervical cancer by age 18.[3] While the percentages in Table 2 are respectable, better adherence to the ACS recommendations would increase the rates of testing.

Table 1. Cancer Type Prevalence by Sex and Stage at Diagnosis

Cancer Type	Total (n = 418), %	Sex % Within Sex: Male (n = 184)	Sex % Within Sex: Female (n = 234)	Stage at Diagnosis % Within Cancer Type: Localized	Regional/ Distant	Unknown or Unstaged
Breast (n = 139)	33	2	58[a]	63	35	3
Prostate (males only) (n = 89)	21	48	0	85	11	3
Skin/melanoma (n = 72)	17	22[a]	14	82	15	3
Colon/rectal (n = 39)	9	12	7	44	54	3
Bladder/kidney/genitourinary (n = 35)	8	17[a]	2	80	20	0
Leukemia/lymphoma (n = 31)	7	8	7	32	39	29
Thyroid (n = 29)	7	3	10[a]	55	38	7
Lung/bronchus (n = 18)	4	5	4	67	33	0
Head/neck (n = 13)	3	3	3	54	46	0
Ovarian (females only) (n = 12)	3	0	5	42	50	8
Uterus (females only) (n = 9)	2	0	4	56	33	11
Cervix (females only) (n = 8)	2	0	3	88	12	0
Pancreas (n = 3)	1	1	0	33	67	0
Gastrointestinal/stomach (n = 3)	1	1	1	0	100	0
Other (n = 16)	4	5	3	81	19	0

[a]Denotes a statistically meaningful difference between columns/rows (+/- 10% at the 95% confidence level).

Cancer Treatment and Goals

Type of Treatment

The type of cancer therapy varied greatly due to the variety of cancer types and cancer stages that were represented in this survey. Treatment modalities included:

- Surgery, 79%
- Radiation, 51%
- Chemotherapy, 40%
- Investigative therapy, 8%
- Supportive therapy, 7%
- Other, 8% (50% of those reported hormonal therapy)

Excluding surgery, patients with regional/distant cancers were significantly more likely to have all modalities of treatment than those with localized cancers. A total of 57% of patients reported more than 1 type of cancer treatment. Among patients receiving multiple treatments, 21% had surgery and radiation; 20% had surgery, radiation, and chemotherapy; and 12% had surgery and chemotherapy. Younger patients were more likely to receive surgery, radiation, and chemotherapy.

Table 2. Tests and Screenings for Cancer

Test/Screening	N	Prior to Diagnosis, %	Since Diagnosis, %
Cervical HPV testing	234 (females only)	28[a]	20
Colonoscopy for colorectal cancer	418	58[a]	43
Test for blood in stool for colorectal cancer	418	48[a]	34
Sigmoidoscopy for colorectal cancer	418	21[a]	12
Mammography for breast cancer screening	234 (females only)	89[a]	74
Oral cancer screening by dentist	418	47	45
Papanicolaou (Pap) test for cervical cancer	234 (females only)	89[a]	67
PSA blood testing for prostate cancer	184 (males only)	85	83
Skin checks by dermatologists for skin cancer	418	57	57

HPV indicates human papillomavirus; PSA, prostate-specific antigen.
[a]Denotes a statistically meaningful difference between columns/rows (+/- 10% at the 95% confidence level).

Chemotherapy Experience

Of those who received intravenous (IV) chemotherapy, most received treatment in a hospital outpatient department (41%), followed by a doctor's office (31%), an infusion center separate from the hospital or doctor's office (28%), and at home (1%). These percentages were similar to those obtained in a 2010 survey by Eisai,[4] with 1 exception. Current data indicate a significant increase from 2010 (14%) to 2012 (28%) in the percentage of patients receiving IV treatment at infusion centers.[4] Free-standing ambulatory infusion centers operate essentially as doctors' offices, but infusions are provided pursuant to a physician's orders and are performed and managed by a registered nurse and registered pharmacist. This trend is expected to increase, as specialty pharmacies have invested heavily in infusion centers (and home infusion centers). Whether the increased share in infusion centers will lead to a significant reduction in hospital outpatient use remains to be seen, but it is expected that it will.

Patients were generally satisfied where they received IV chemotherapy. Still, those receiving infusions at a doctor's office reported slightly higher levels of satisfaction than those receiving treatment at a free-standing infusion center. Patients receiving oral or self-injectable chemotherapy delivered by a specialty pharmacy or a mail order pharmacy reported the highest level of satisfaction. Data suggest improvement opportunities with in-office pharmacies and local retail pharmacies.

Goals of Treatment

Respondents' answers to goals of treatment varied. A total of 69% of patients reported remission as their goal, whereas 44% and 31% stated prolonged life and preserved quality of life, respectively. Surprisingly, patient age was not correlated with goal of treatment. However, the stage of cancer influenced goal of treatment (**Figure**). The top chosen treatment goal among patients with distant cancers was prolonged life. Despite the perception that these patients tend to receive only palliative care for improved quality of life, it is an important finding that many have chosen extended survival as their goal.

Conclusion

The *2012 Eisai Oncology Digest* provides healthcare professionals with valuable insight on how patients with cancer view their treatment. High rates of screening were associated with common cancers, but results indicate that there is room for improvement and better adherence to guidelines. Most patients have the treatment goal of cancer remission. However, the primary goal of patients with more advanced cancer is prolonging life. Knowledge of these goals may influence how physicians approach the treatment and management of localized versus advanced cancers in the future.

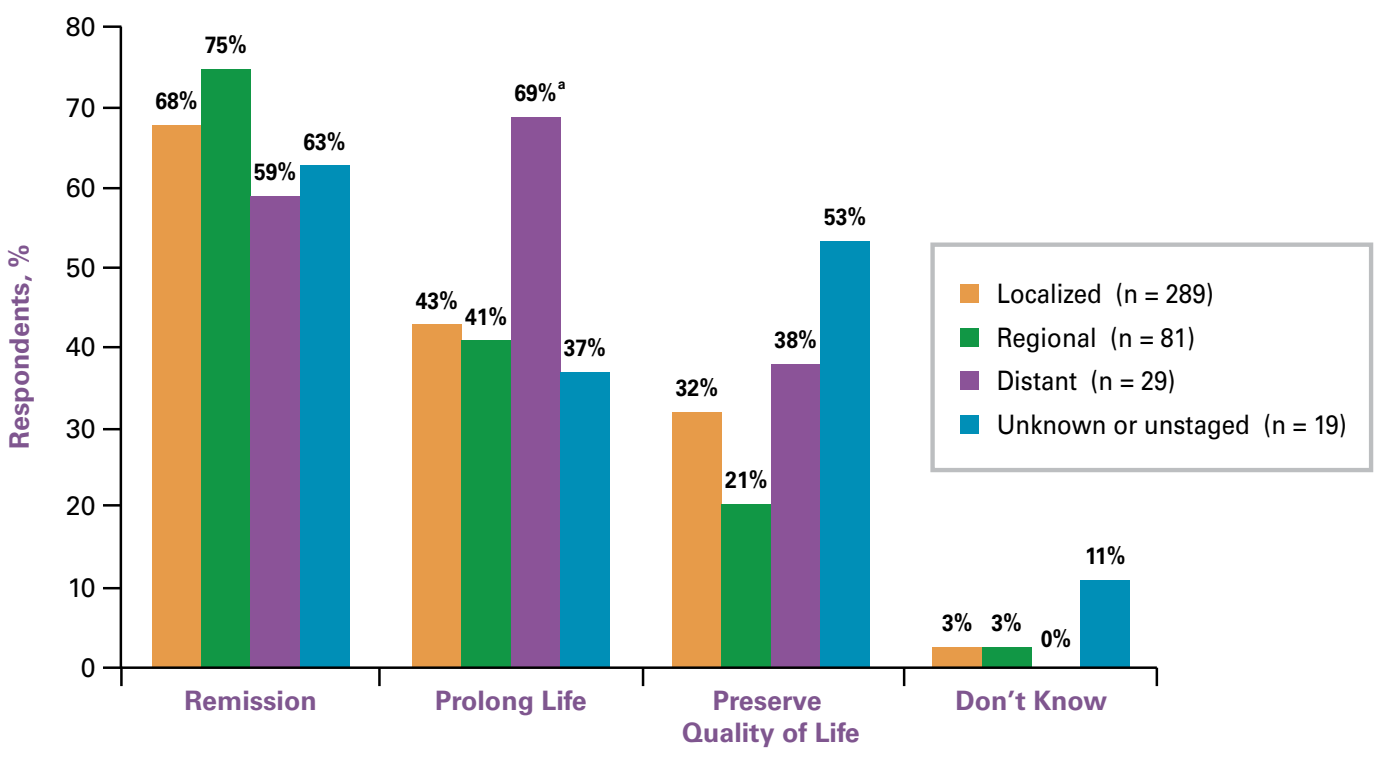
Although patients were given chemotherapy in varied settings, most were satisfied with how they received medication. This topic will be explored further in the second article in this series, which will detail how respondents felt about the quality of their care and counseling/communication. The final article in this series will describe insurance and cost obstacles that patients encountered during treatment. **EBO**

High rates of screening were associated with common cancers, but results indicate that there is room for improvement and better adherence to guidelines.

References

1. *2012 Eisai Oncology Digest*. Woodcliff Lake, NJ: ReCon Marketing Solutions, LLC; 2012.
2. Howlader N, Noone AM, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2008. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2008/. Published 2011.
3. Cancer Facts & Figures 2011. American Cancer Society website. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-029771.pdf. Accessed April 13, 2012.
4. *Eisai Oncology and Senior Health Digest*. Woodcliff Lake, NJ: Cooper Research; 2010.

Figure. Goals of Treatment by Cancer Stage



[a]Statistically significant compared with all other stages within the goal of prolonging life.

Oncology with soul

At Eisai, *human health care* is our goal. We give our first thoughts to patients and their families, and helping to increase the benefits healthcare provides. Our therapies and diverse oncology pipeline are designed to help make a difference and have an impact on patients' lives. We are Eisai, where oncology is more than just our business—it's our passion.

Eisai

Oncology

Our passion ignites progress

MULTIPLE MYELOMA

Pre–Transplant Induction, Consolidation, and Maintenance Therapy

For many years, first-line treatment for younger multiple myeloma (MM) patients has involved high-dose chemotherapy as well as autologous stem-cell transplantation (ASCT). The more recent use of lenalidomide, thalidomide, and bortezomib as induction and consolidation therapy has changed the way we approach patients with relapsed and refractory MM, according to Donna E. Reece, MD, from the Princess Margaret Hospital, Toronto, Canada. Dr Reece reviewed the use of innovative therapies before and after ASCT, focusing on phase 3 trial results.

Use in Induction Therapy Before Undergoing ASCT. Newer combinations have been compared with older induction regimens before ASCT in various phase 3 studies, stated Dr Reece. However, outcomes comparisons are challenging, because many of the trials used different maintenance or consolidation treatments, and the induction regimens themselves varied. In phase 3 trials, induction regimens included:

- Lenalidomide and dexamethasone
- Thalidomide and dexamethasone
- Bortezomib and dexamethasone
- Bortezomib, thalidomide, and dexamethasone
- Bortezomib, adriamycin, and dexamethasone
- Vincristine, carmustine, melphalan, cyclophosphamide, doxorubicin, and prednisone

The trials used varying doses of these agents. Dr Reece stated that each of the therapy combinations using novel agents offer benefits over conventional chemotherapy in terms of remission rates. However, only 1 trial not using lenalidomide reported a statistically significant overall survival (OS) rate—when bortezomib was used both before and after ASCT during the HOVON MM-65/GMMG-HD4 study, which enrolled 613 participants and used the induction treatment of bortezomib, adriamycin, and dexamethasone. In this trial, the bortezomib combination was compared with the conventional chemotherapy combination of vincristine, doxorubicin, and dexamethasone, and resulted in a progression-free survival (PFS) at 3 years of 48% and a median 3-year OS of 78% for the study drug combination.

The induction regimen of lenalidomide and dexamethasone was examined by Dr Reece. A phase 3 trial compared lenalidomide plus either high-dose dexamethasone (40 mg on days 1-4, 9-12, and 17-20 on a 28-day schedule) or a weekly low dose (40 mg) for 4 cycles in patients just diagnosed with myeloma. After 4 cycles, the overall response rate for the lenalidomide plus high-dose or low-dose dexamethasone groups was 79% versus 68%, with a "very good partial remission," nearly complete remission, or complete remission rate of 42% versus 24%, respectively. A 92% survival at 3 years was achieved for patients who underwent ASCT. However, she pointed out a possible bias for the ASCT patients due to the design of the study: The individuals undergoing ASCT may have been younger and healthier or high-risk patients who were not presumed to do well with a continued administration of the lenalidomide combination regimen. The data do show, according to Dr Reece, that the combination therapy was well-tolerated and stem-cell collection was not compromised when patients were given chemotherapy and hematopoietic growth factors.

The Total Therapy programs developed by the University of Arkansas are also noteworthy, stated Dr Reece. Newly diagnosed patients were treated with induction therapy consisting of 2 cycles of dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide (D-PACE) in the Total Therapy 2 trial, before tandem ASCT, further D-PACE consolidation, and maintenance with IFN for 1 year and dexamethasone until the disease advanced. They were then randomized to either receive thalidomide or not. Patients in the thalidomide group experienced higher remission rates before and after ASCT and a significantly longer progression-free survival (PFS). The next study, Total Therapy 3, added bortezomib, thalidomide, and dexamethasone (VTD) as VTD-PACE, which patients received before and after ASCT. This regimen led to a further improvement in the response rate, OS, and PFS for newly diagnosed patients with low-risk disease, but Dr Reece noted that approximately 15% had early treatment failure and death. Therefore, it is still a challenge to find optimal treatment for this subset of patients.

All of the various study regimens using novel agents were proved to be superior in attaining higher response rates after induction therapy, according to Dr Reece.

Maintenance Therapy. The most frequently studied maintenance drugs are lenalidomide and thalidomide. Seven randomized trials of post-ASCT thalidomide therapy were analyzed by Dr Reece. They were different with regard to use of induction regimen, single or tandem transplantation before starting maintenance therapy, thalidomide dose and duration, corticosteroid use, and comparison with various regimens. Even so, a PFS benefit was consistently seen with thalidomide therapy (OS benefit was not always observed).

The optimal use of thalidomide maintenance is still unclear, Dr Reece admitted, because of different criteria used when classifying patient subgroups even after several investigators attempted to identify which patient groups would most likely benefit from this therapy. Nevertheless, thalidomide maintenance therapy has not been widely accepted outside of clinical trials even with the longer PFS, said Dr Reece, largely owing to its toxicity.

Maintenance therapy with lenalidomide has also recently been studied. The CALGB-100104 study in North America and the IFM 2005-02 trial in France compared low doses of lenalidomide (10-15 mg/day) with placebo after ASCT. Both studies demonstrated a median PFS of 42 months in the lenalidomide groups.

Unexpectedly, a fairly small increase in the frequency of secondary cancers, such as secondary myelodysplastic syndromes and/or acute myelogenous leukemia, was observed in both studies, Dr Reece pointed out, but the risk is "quite small and is likely counterbalanced by the strong anti-myeloma efficacy of this drug when used in the maintenance setting."

Consolidation Therapy. Three recent phase 3 trials examined consolidation therapy use after ASCT. Some of the best outcomes of a transplantation program so far, according to Dr Reece, were from an Italian trial that used the bortezomib-thalidomide-dexamethasone regimen, also given for induction for 2 cycles after transplantation while a control group did not receive bortezomib for 2 months. In the IFM-2005-02 trial, patients were given a full therapeutic consolidation dose of lenalidomide (25 mg for 2 cycles) followed by a lower maintenance dose until disease progression. The ASCT patients in the Nordic Myeloma Study Group were randomized to receive bortezomib treatment or no therapy. Both of those groups had a 90% OS. Each innovative agent can postpone disease progression, noted Dr Reece, as demonstrated in these post-ASCT maintenance and/or consolidation studies even when OS benefits have not been found.

Novel agents used at the induction phase followed by maintenance with lenalidomide after ASCT have the best PFS results so far, concluded Dr Reece. She added that the role of a second ASCT or consolidation therapy to lenalidomide maintenance is still to be clarified by clinical trials. **EBO**

Nevertheless, thalidomide maintenance therapy has not been widely accepted outside of clinical trials even with the longer PFS, largely owing to its toxicity.

Source: Reece DE. Post-transplantation maintenance therapy and optimal frontline therapy in myeloma. *Hematology Am Soc Hematol Educ Program*. 2011;2011:197-204.

THE AMERICAN JOURNAL OF MANAGED CARE

Benefits of Lenalidomide Dose Reduction for Patients With Multiple Myeloma

A combination of lenalidomide and dexamethasone is indicated for use in patients suffering from relapsed or refractory multiple myeloma (MM) who had tried at least 1 previous treatment. This approval was based on the results of 2 phase 3 clinical trials, which also showed that continuing, long-term therapy assures patients the best chance for success. However, the evidence supporting the optimal dose of lenalidomide in patients with recurrent or refractory MM is vague. Full dosing (25 mg/day) is associated with common adverse effects, which can result in delays in or interrupted treatment. Clinicians from Greece and the United States sought to determine from the 2 pivotal trials whether reduced doses of lenalidomide had a negative effect on progression-free survival (PFS).

The study group included only subjects who did not progress and were still being treated with lenalidomide 12 months after starting therapy. Of the 177 patients in the MM-009 trial receiving lenalidomide and dexamethasone and 176 from the MM-010 trial, 116 were included in the analysis. A total of 52 patients (45%) had no dose reductions, 39 (34%) had their lenalidomide dose reduced before 12 months, and 25 (22%) had their lenalidomide reduced at least 12 months after starting therapy.

All 3 subgroups achieved similarly high response rates. However, a significantly longer PFS was seen in patients with dose reductions after 12 months than those with dose reductions before 12 months or those with no dose reductions. For those with dose reductions 12 months or beyond, PFS was not yet reached. In comparison, for those without any dose reduction, median PFS was 36.8 months (P = .039). None of the 3 subgroups reached median overall survival.

After adjusting for patient characteristics, a Cox regression analysis of PFS found that an independent predictor of PFS continued to be lenalidomide dose reductions after 12 months (hazard ratio, 0.47; 95% confidence interval, 0.23-0.98). Twelve-month levels of serum albumin, M-protein, and neutrophils were other independent predictors of PFS.

The patients who had lenalidomide dose reductions after at least 12 months of full-dose lenalidomide experienced a significantly higher median PFS as well as overall survival than those who had dose reductions earlier, the researchers commented. Therefore, they added, the data suggest if the patient can tolerate the treatment, it is important that the full-dose lenalidomide therapy should continue for at least 12 months. **EBO**

Source: Dimopoulos MA, Hussein M, Swern AS, et al. Impact of lenalidomide dose on progression-free survival in patients with relapsed or refractory multiple myeloma. *Leukemia*. 2011;25:1620-1626.

Can Reduced Lenalidomide Doses in Refractory or Recurrent Multiple Myeloma Patients Produce Positive Outcomes?

Lenalidomide combined with dexamethasone has proved to be an effective treatment for many patients with refractory or recurrent multiple myeloma (MM). German researchers noted, however, that adverse effects seen with the approved doses (25 mg/day for 21 days of each 28-day cycle) may result in suboptimal cancer outcomes in some individuals.

They evaluated the efficacy of a reduced lenalidomide dose on 10 patients with recurrent MM who had difficulty adhering to standard dosing because of leukopenia (4 patients), muscle cramps (1), polyneuropathy (1), renal insufficiency (1), or thrombocytopenia (1). In 1 case, the patient requested the reduced dose and in another, the patient was given lenalidomide as reduced-dose continuous therapy (1). Two patients began the trial with a reduced dose while 8 had their dose reduced during the therapy. Seven patients had undergone autologous stem-cell transplant, and all had had at least 2 previous MM treatments.

Initially, 8 subjects received the full 25-mg per day lenalidomide dose on days 1 to 21 every 28 days plus dexamethasone at a mean dose of 17.6 mg per day on days 1 to 4, 9 to 12, and 17 to 20, with the dose first reduced a mean of 4.8 months after beginning treatment. After dose reduction, lenalidomide averaged 14.1 mg per day. Treatment duration with lenalidomide averaged 15.1 months.

One study participant achieved a complete response, 6 attained a partial response, and 1 had a minimal response. Time to first response after starting lenalidomide was a median 41.1 days. The dose each patient was taking at the time of their best response was 25 mg per day in 7 patients (1 complete response, 5 partial responses, 1 progressive disease), 15 mg per day in 1 patient (partial response), 10 mg per day in 1 patient (who experienced progressive disease), and 5 mg per day in another (who experienced minimal response only). Therefore, most of the patients in this small series experienced best response before their dose was reduced; however, they continued to do well after the dose reduction.

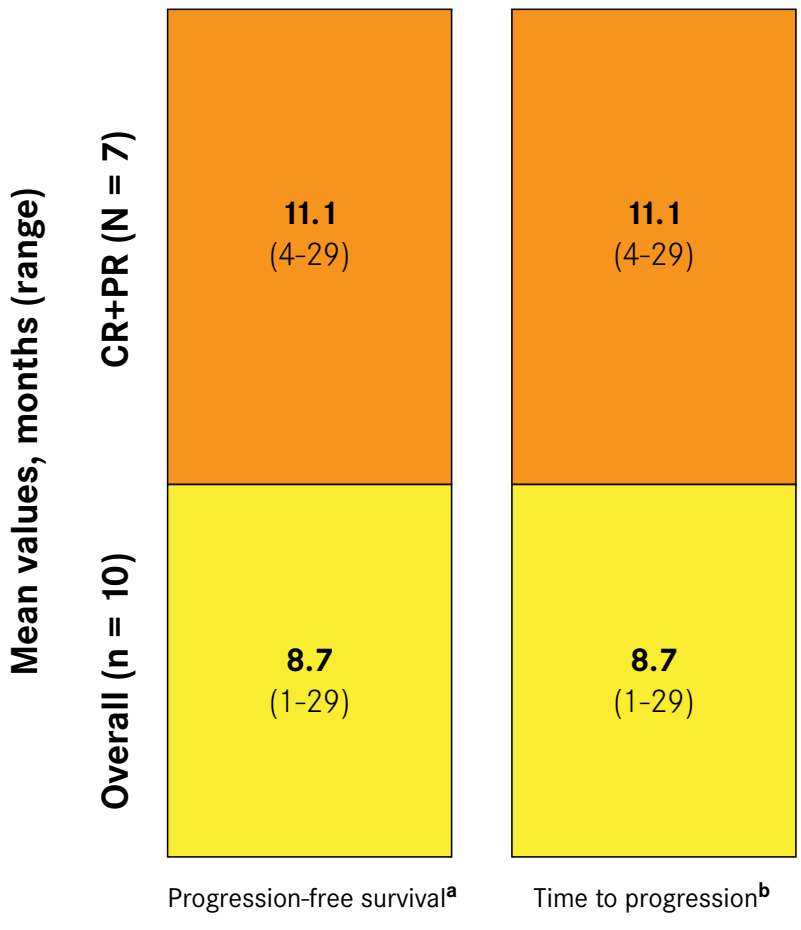
The time-to-progression (TTP) mean values and progression-free survival (PFS) rates are noted in the **Figure**. Both were 8.7 months. Since all patients were still alive at the end of the study, a mean overall survival could not be calculated.

All patients experienced some level of anemia (grade 3/4, 2 patients), and leukopenia was observed in 8 (grade 3, 3 patients), thrombocytopenia in 7 (grade 3, 3 patients). When the lenalidomide dose was decreased, thrombocytopenia, anemia, and leukopenia became stable or diminished. Non-hematologic toxicities included back pain (5 patients), polyneuropathy (3), muscle cramps (2), pruritus (1), and severe constipation (1).

The researchers concluded that in patients who experienced recurrent or refractory MM and who could not tolerate a standard dose of lenalidomide, dose reductions still proved to be a safe and effective alternative. **EBO**

Source: Schwamborn K, Gorschluter M, Glasmacher A, et al. Efficacy of dose-reduced lenalidomide in patients with refractory or recurrent multiple myeloma. *GMS Ger Med Sci*. 2011;9:doc26.

Figure. Progression-Free Survival and Time to Progression



CR indicates complete response; PR, partial response.
[a]Up to the time of data collection all patients were still alive.
[b]The disease did not progress in 3 patients by study completion.
Adapted from Schwamborn et al. *GMS Ger Med Sci*. 2011;9:doc26.

THE AMERICAN JOURNAL OF MANAGED CARE

Commentary SP139

Cancer Care Value—Learning From Others

Getting Smarter in How We Score and Promote Value

Robert "Bo" Gamble

As of March 2, 2012, there were 395,000 available apps for the Android phone, with 278,000 of those being free.[1] The iPhone has over 578,000 as of February 27, 2012, with 222,000 free.[2] The developers seem to have it figured out. I tend to pursue "free" apps only, but then find myself spending tens of dollars in fighting and avoiding advertisements. The $0.99 app of the same is likely free of such and therefore a valuable saver of time: the most precious resource. I also find it very ironic that even the "free" apps get reviewed and scored. It is very rare that we are asked to rate or score free items. Can you imagine driving down the interstate entering another state and suddenly being asked to evaluate the air—and not being able to leave the state or use an exit ramp until you do.

A recent evening snack also reminded me of another value "trick" that has befallen us: the beloved "half gallon" of ice cream that is no longer. The typical size of a carton of ice cream is now 1.75 quarts—a reduction of 1/8. When did that happen, and which rock have I been under? And it is not just ice cream. Candy bars, coffee, and toilet paper are further examples of lowering the quantity without lowering the price. The next evolution of these marketers is increasing the size with a greater than proportional price increase and calling it a "value size."

Another example is the flood of commercials for gold, from "sell your grandmother's gold to us for the best price" to celebrities telling how they have converted all of their assets to gold. I was perplexed with all of the sudden interest in these nuggets from the earth. It then dawned on me that all of this recent activity was created by the Gold Sellers Union in order to push up the demand for gold and thus increase the price. After all, isn't there a limited supply of gold?

When pondering the value of cancer care and how it is determined, I was struck by the difficulty of creating, defining, and promoting the value of quality cancer care. If we try learning from other industries, we should be able to do something like the following:

"Our cancer treatment was voted best by all cancer patients and their families. Use our free treatment or upgrade to our less-advertised version of treatment for only $10,000." The advertisers would be

Robert "Bo" Gamble

subsidizing all of the treatments, free or not, and the subsidy would come from pharmaceutical companies, supply vendors, et cetera. Oooops, I forgot, this has already been determined to be illegal. Again, too much time for me under the rock.

Applying the above to our world, we could reduce the usual dose for specific cancer treatments, continue to promote that treatment, and then increase the dose to normal amounts and follow with promotions of "Value Dose." Yep, you are right, not a good idea, and counterproductive to what we are here to do.

We do seem to have a real example of how increasing the demand does not necessarily increase the price. Consider the ongoing chemotherapy drug shortage issues. Most of current shortage drugs are generic, typically the least expensive in their class. Spontaneous increases in their costs, for regulatory or production reasons, are not matched with provider reimbursement due to the 6-month lag built into the ASP reimbursement system. This is an unexpected result of implementing unnatural forces into a world that is accustomed to natural market forces.

So why is it so hard to define, measure, and promote "value" in cancer care? My healthcare marketing professor said it best in describing the uniqueness of healthcare. It is one of the only industries where the consumer, decision maker, and purchaser are 3 different people. (This coming from the same professor that indicated Ferrero, the manufacturer of TicTacs, was actually selling "fun" and not breath mints.) The major stakeholders in our world are the patient (the consumer), the provider (the decision maker), and the payer (the purchaser). Each has their own list of priorities as well as their own subset of stakeholders. Upon close review, their priorities seem similar but not necessarily aligned.

Cancer patients are supported by their families, friends, and employers. According to a recent gathering of major stakeholders, the things patients desire from the care team include access, ability, affordability, affability, and availability. They also anticipate quality and timely communications, honesty, and the best possible outcome with the best possible quality of life. Additionally, they request the least amount of pain, toxicity, and test results.

Providers are not much different. They are surrounded by clinicians, advocate organizations, and networks of other providers and diagnostic facilities. They also want satisfied patients and families, best possible outcomes, minimized administrative burdens, a fair reimbursement for all of the services provided, and positive incentives to continue all of the above. Quality of life is paramount.

And are payers much different? It does not sound like it. Although they are accountable to their stockholders or taxpayers, they also desire similar outcomes. They want member satisfaction, the best possible clinical outcome, the highest quality care in the lowest cost setting, treatments for members that are cost-effective and evidence-based, and meaningful indicators of quality and value.

The common threads between these 3 major groups of cancer care stakeholders are patient and family satisfaction and measurable value. The challenge is to define these attributes so that they are measurable, relative, and aligned between all care providers and stakeholders. We do not have the luxury of being able to call on advertisement sponsorship, or to adjust the package size, or to artificially inflate demand—nor would we want to. So then, how do we become united in our efforts, definitions, and recognition?

The recent gathering of 16 representatives from the various stakeholder groups is a great start. These individuals have crossed competitive lines from their payer, provider, or group purchasing worlds to collaborate on solutions that will benefit the patients, their families, and one another. They recently met in Atlanta to collectively address this issue with collaborative, open, and honest communications. The goals are evident and obvious but the obstacles are real. Standardizing and measuring patient and family satisfaction is the simpler of the 2 and great strides have been made to implement and report this information across all specialties. However, the value proposition is much more difficult. One payer said it best—they cannot easily and arbitrarily pay a single provider group for higher quality or value. Everything has a cost, even in the above-mentioned scenarios. Our approach should be no tricks but instead transparent positive incentives to encourage, promote, and recognize quality and value. The industry leaders that were seated at the table on those 2 days believe that this can be accomplished and in a way that all stakeholders may benefit. Once the value proposition is defined, we will be able to redefine age-old payment systems so that all value and quality will be evident and rewarded. Are we there yet? Not yet, but if the same creative and passionate minds that are working on this issue were also involved in the ice cream decisions, we might still have a full half gallon of cookies and cream. **EBO**

Author Affiliation: From Strategic Practice Initiatives, Community Oncology Alliance, Washington, DC.

Funding Source: None.

Author Disclosure: The author reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; administrative, technical, or logistic support; and supervision.

References

1. AppBrain website. http://www.appbrain.com/stats/. Accessed March 9, 2012.

2. 148Apps.Biz website. http://148apps.biz/app-store-metrics/. Accessed March 9, 2012.

THE AMERICAN JOURNAL OF MANAGED CARE

On the Horizon for Multiple Myeloma

Availability of Newer Agents May Lower Healthcare Costs

Michael Marlan Mohundro, PharmD; and Brice Labruzzo Mohundro, PharmD

Treatment of multiple myeloma (MM) remains highly individualized, with multiple factors that play a role in determining the best course of therapy. Patient-specific criteria such as age of onset, whether the patient is symptomatic at the time of diagnosis, and any detected high-risk cytogenic abnormalities are all considerations when selecting a regimen. Newer agents such as bortezomib and lenalidomide in combination with low-dose steroids have replaced more toxic chemotherapeutic regimens for primary induction and have led to significant increases in progression-free survival. Depending on duration of response prior to relapse, patients may be rechallenged with the same regimen, switched to an alternative, or may undergo hematopoietic cell transplant (HCT), which remains a highly effective treatment option for patients who are candidates. However, the cost of transplantation remains high and some patients may require a second transplantation if the initial response is incomplete. With the availability of newer agents for salvage therapies in refractory or relapsed patients, the reliance on HCT may decrease, potentially lowering healthcare costs. In addition, the availability of orally active agents may decrease the need for outpatient infusions, thus decreasing the overall costs associated with treatment and improving patient satisfaction. Finally, combination regimens that use lower doses may prove to be less toxic as well as more effective. Even though MM only accounts for approximately 1% of all cancers in the United States, with 75 million "baby boomers" now reaching the median age of diagnosis, the increased number of cases could have a substantial impact on healthcare costs.

MM is a fairly uncommon cancer, comprising only 1% of cancer in the United States; however, it is the most commonly occurring blood cancer.[1] The American Cancer Society estimates that in 2012, approximately 21,700 new cases will be diagnosed and approximately 10,710 deaths will occur as a result of MM.[2] Patients with MM may present with bone pain (especially in the back), fatigue often caused by anemia, pathologic fracture, weight loss, and/or paresthesias. Some patients have no symptoms at the time of diagnosis.[3] MM occurs when vast amounts of abnormal plasma cells are found in bone marrow. Additionally, there is an overproduction of IgG, IgA, IgD, IgE, or monoclonal light chains known as Bence-Jones proteins.[4] Treatment of MM is complex. Patients with stage II or III myeloma who are considered to have good performance status are candidates for stem cell transplantation. Induction therapy with dexamethasone monotherapy or a combination of dexamethasone and thalidomide before stem cell harvesting is an option for patients; however, high-dose chemotherapy with vincristine, melphalan, cyclophosphamide, and prednisone alternating with vincristine, carmustine, doxorubicin, and prednisone along with bone marrow transplant has been associated with increased survival in patients. Patients who are not stem cell candidates may be treated with thalidomide, melphalan, and prednisone. Patients who are not responding or who relapse with this regimen may be treated with vincristine, doxorubicin, and dexamethasone.[5] Refractory or relapsing MM is common. Currently, regimens available for these patients contain thalidomide, lenalidomide, or bortezomib. On the horizon to treat patients with relapsed or refractory myeloma are a new generation of proteasome inhibitors, immunomodulatory agents, and deacetylase inhibitors which are currently being investigated in clinical trials.

Immunomodulating Agents

Despite MM being an incurable disease, immunomodulatory drugs (IMiDs) have demonstrated effectiveness in the treatment of MM. IMiDs have been investigated for both first-line and maintenance therapies.[6] Thalidomide was the first drug in this class and subsequently lenalidomide was approved by the US Food and Drug Administration (FDA).[6] Pomalidomide is the newest IMiD under investigation and several phase I and II trials have been completed. While the drug is a chemical analogue of thalidomide, it appears to have a much greater potency in stimulating the proliferation of T-cells as well as increasing natural killer cell activity.[6] Additionally, the drug works through inhibition of blood cell growth and modulates the levels of inflammatory and regulatory cytokines. IMiDs have also been shown to directly induce apoptosis in plasma cells.[6] Phase I, II, and III clinical trials are currently under way to evaluate the drug in combination with dexamethasone, as well as in combination with bortezomib, doxorubicin, and cyclophosphamide.[7]

Proteasome Inhibitors

Proteasomes serve as valuable chemotherapeutic targets due to the integral role they play in protein homeostasis, degradation of cytotoxic proteins, and clearance of misfolded and/or unfolded proteins.[8] Key proteins regulated by proteasomes that are involved in cell-cycle progression and apoptosis include cyclins, caspases, B-cell lymphoma 2 (BCL2), and NF-B activation.[8] It is believed that malignant cells are more dependent on this cellular housekeeping, and this is supported by several studies indicating that cancer cells are more susceptible to proteasome inhibition.[8] In 2003, bortezomib became the first drug in this class to be approved by the FDA for initial MM treatment and relapsed/refractory MM; however, drug resistance and dose-limiting toxicities such as peripheral neuropathy remain a concern with bortezomib treatment.[9,10]

Carfilzomib

Carfilzomib, an epoxyketone, is a structural analogue of the natural microbial product epoxomycin-3.[11] This novel proteasome inhibitor has a structure and mechanism different from bortezomib.[11] Carfilzomib differs by being an irreversible inhibitor as opposed to the reversible inhibition seen with bortezomib, which gives carfilzomib a longer duration of inhibition.[11] It also appears to be more specific in its affinity for chymotrypsin-like protease, with lesser activity seen for the trypsin and caspase-like proteases in the 26S proteasome.[11] Currently, carfilzomib is being evaluated in phase III clinical trials with lenalidomide and low-dose dexamethasone in patients with relapsed MM.[12]

MLN9708

MLN9708 is an orally active, reversible proteasome inhibitor chemically distinct from bortezomib that is currently in multiple phase I and II clinical trials.[13] In vitro and in vivo studies revealed MLN9708 had an improved volume of distribution, greater inhibition of the proteasome, and thus a greater anti-tumor effect than bortezomib.[13] It works by increasing the number of ubiquinated proteins selected for destruction, leading to cell cycle disruption and the activation of apoptotic pathways. MLN9708 caused cell death in both a time-dependent and dose-dependent fashion, and the drug increased survival with continuous or intermittent administration. Further studies are needed to assess its place in therapeutic regimens, but currently recruiting phase I and II studies are evaluating MLN9708 with lenalidomide and dexamethasone, melphalan, and prednisone, and in patients that have relapsed with bortezomib treatment.[14]

Marizomib

Marizomib is an orally active, novel, irreversible proteasome inhibitor that is also distinct from bortezomib. In preclinical trials marizomib demonstrated a synergistic cytotoxic effect when used in combination with IMiDs such as lenalidomide. Toxicity has been a concern with bortezomib therapy; however, lower doses of IMiDs and marizomib used together in studies revealed minimal toxic effects. Marizomib has shown that it can trigger cell death in MM cells in the presence of bortezomib resistance.[10] Phase I marizomib studies are ongoing and include subjects with relapsed or refractory MM.[15]

CEP-18770

CEP-18770 is a reversible proteasome inhibitor with the potential to be administered orally, but was also dosed via the intravenous route during studies. Preclinical trials have been done with the drug when used as monotherapy, as well as in combination with bortezomib and melphalan. Synergy was demonstrated in studies with the combination regimens. Investigators were able to show that sensitization of previously resistant tumors was induced by co-administration of CEP-18770. CEP-18770 studies have established a good safety profile, with 10-fold

greater than therapeutic concentrations showing little or no effect on normal human epithelial cells, BM progenitors, BM-derived stromal cells, and PBMCs.[16] CEP-18770 has 2 studies enrolling at the time of this article on clinicaltrials.gov, with 1 study involving combination treatment with dexamethasone and lenalidomide and the other to further investigate maximum tolerated dose (MTD) as well as safety and efficacy in relapsed MM refractory to the most recent therapy.[17]

Deacetylase Inhibitors (DACi)

Deacetylase (DAC) inhibitors, previously referred to as histone deacetylase inhibitors, demonstrate much farther reaching effects than histone deacetylation (HDAC) alone.[8] There are 4 classes of DAC enzymes that have been classified, with 18 specific enzymes that were identified in humans.[8] Class I DAC enzymes are found locally within the nucleus of the cell while class II can be found in multiple locations, including the nucleus and cytoplasm.[8] Preclinical studies using several DAC inhibitors in both in vitro and in vivo mouse xenograft models have demonstrated inhibition of cell proliferation and induction of apoptosis of MM cells.[8] However, phase I trials have shown limited viability of the class to be useful in single-agent treatment of MM.[8]

Romidepsin

Romidepsin is a cyclic tetrapeptide FDA-approved for the treatment of T-cell lymphoma.[8,18] Previously, it was thought to only affect class I DAC enzymes, but at higher concentrations it inhibits activity of the class II enzymes as well.[18] Early preclinical trials have demonstrated romidepsin's efficacy against a variety of MM cell lines. An investigation has now been completed using romidepsin in combination with dexamethasone and bortezomib.[18] Results from this small study indicate that the combination had sustained results, with a median time to progression of 7.2 months, and 3 patients that exceeded 20 months. While the groundbreaking APEX bortezomib trial had a median survival of 29.8 months, at the time of the publication the cohort had a median survival of greater than 36 months, with the 1-year survival in a heavily pretreated group being 76%.[18] Enrollment is currently being sought for a Phase I/II clinical trial involving bortezomib and romidepsin in patients with relapsed myeloma.[19]

Panobinostat

Panobinostat is a novel, hydroxamic acid–based DAC inhibitor that exhibits broad inhibitory activity. It has shown activity toward class I, II, and IV HDAC and is perhaps the most potent inhibitor identified to date.[8] Benefits have been seen in patients with refractory hematologic malignancies, and currently, a phase III clinical trial is under way to evaluate panobinostat in combination with bortezomib and dexamethasone in relapsed MM patients.[20,21] Additional phase I and II trials are also under way, including combination with immunomodulators and other proteasome inhibitors.[21]

Vorinostat

Vorinostat is a DAC inhibitor that is FDA-approved for certain lymphomas and has a broad spectrum of activity toward class I, II, and IV HDACs.[8] The drug works by decreasing the rate of myeloma cell proliferation and induces apoptosis by increasing the production of proteins involved in those processes. However, results from a large phase III clinical trial and a phase IIb trial demonstrated disappointing results, raising doubts whether vorinostat will get FDA approval for MM indications.[22]

Monoclonal Antibodies (mAbs)

Monoclonal antibodies (mAbs) have demonstrated favorable results in a variety of cancers (eg, trastuzumab in breast cancer, bevacizumab in renal cell carcinoma, and cetuximab in squamous cell carcinoma).[23] While the mechanism of action of the mAbs has not been fully elucidated, they have been shown to induce antibody-dependent cell-mediated cytotoxicity (ADCC) and directly cause cell death through signal transduction.[23]

Siltuximab

Siltuximab is a chimeric human-mouse mAb that works by neutralizing interleukin-6 (IL-6). IL-6 is secreted predominantly by bone marrow stromal cells (BMSCs) which activate a series of survival and proliferative pathways in myeloma cells.[23,24] Patients that have high serum levels of IL-6 have been shown to have a poor prognosis. Within the microenvironment of the bone marrow, MM cells attach to BMSCs, and the adhesion stimulates the secretion of IL-6 and other pro-survival cytokines.[23,24] In preclinical trials, siltuximab has demonstrated positive results when tested together with bortezomib, dexamethasone, and melphalan.[23] However, a phase III trial evaluating siltuximab with bortezomib and dexamethasone was withdrawn from ClinicalTrials.gov before recruitment began.[25]

Elotuzumab

Elotuzumab is a humanized mAb targeted against the cell surface glycoprotein CS1, which is highly expressed on MM cell lines including over 97% of the cells of patients with MM. The primary mechanism of action of elotuzumab is through NK cell-mediated ADCC. Studies have also indicated that elotuzumab works by blocking myeloma cell binding to BMSCs, which is believed to diminish the stimulatory effects on the growth and survival of MM cells. Results from a phase I trial that evaluated the combination of elotuzumab and bortezomib suggest that the combination warrants further investigation due to the positive results demonstrated in the study and a phase II trial is planned. Currently, a phase III clinical trial (ELQUENT-2) is under way to assess the combination of elotuzumab with lenalidomide and dexamethasone in patients with relapsed MM.[26]

Dacetuzumab

Dacetuzumab is a humanized mAb that is targeted against the CD-40 receptor, which has been noted to be overexpressed on MM cells, as well as BMSCs.[23,27] Dacetuzumab works through multiple mechanisms of action, including the induction of cell death through direct signal transduction, as well as antibody-dependent cellular cytotoxicity and phagocytosis.[27] Results of phase I trials suggest that, while the drug is relatively safe and well tolerated, its role as monotherapy has only shown modest promise. In vitro trials demonstrated a synergistic effect with lenalidomide that perhaps will lead to better response rates.[27]

Atacicept

Atacicept is a unique fusion protein consisting of both the extracellular ligand-binding portion of the TACI receptor and the Fc portion of human IgG. The drug acts by neutralizing 2 key proteins of the Tumor Necrosis Factor (TNF) ligand family that are vital for the growth and development of B cells. Interaction of atacicept with the target receptors has antiproliferative effects and leads to apoptosis of myeloma cells. Primary receptor targets are B-lymphocyte stimulator (BLys) and A proliferative-inducing ligand (APRIL). Both of these receptors produced in significant amounts in the microenvironment of the bone marrow and myeloma cells abnormally express BLys and APRIL mRNA. Trans-membrane activator and CAML interactor (TACI) and B-cell maturation antigen (BCMA), which are found on most myeloma cell lines, are receptors shared by both BLys and APRIL. In preclinical trials, subcutaneous atacicept was well tolerated and found to be relatively safe. However, due to the suppression of polyclonal B cells, infection remains a possible serious adverse effect despite the lack of occurrence during the initial trial. Currently, there are no clinical trials under way; however, the drug remains a target of interest.[28]

Perifosine

Perifosine belongs to a new class of antineoplastic agents that work through Akt inhibition in the PI3K pathway. The drug is a synthetically derived alkylphospholipid that is currently in phase I clinical trials. It has been found to be orally active and works at the cell membrane of MM cells to trigger apoptosis. Apoptotic pathways initiated by perifosine are believed to be facilitated by caspase-8, caspase-9, poly (ADP-ribose) polymerase (PARP) cleavage. In studies, it has been shown to enhance inhibition of cell growth and cytotoxicity in combination models, including the mainstay of treatment with dexamethasone, as well as doxorubicin, melphalan, and bortezomib. Two key mechanisms of drug resistance that limit effectiveness of dexamethasone are the upregulation of IL-6 and IGF-1. However, in vitro studies using these exogenous cytokines were unable to diminish the cytotoxic effect of perifosine. Additionally, the protective effect seen with the attachment of myeloma cells to BMSCs was not demonstrated with perifosine exposure. Combined with in vivo studies using mouse models showing inhibitory cell growth and prolonged survival, the drug shows great promise both as monotherapy and in combination with other agents.[29] Currently, phase I trials are seeking enrollment to evaluate perifosine in combination with dexamethasone and bortezomib and another trial will investigate perifosine used in combination with dexamethasone and lenalidomide.[30]

Despite these new agents on the horizon, MM needs to remain a target for new drug development to help overcome the high relapse rates and refractory disease associated with this cancer.

Heat Shock Protein 90

Heat shock protein 90 (Hsp90) has long been recognized as a molecular target for drug development, but has only recently aroused significant clinical and pharmaceutical interest.[31] Hsp90 is an ATP-dependent chaperone protein that plays an important role in the promotion of proliferation, as well as malignant cell survival.[32] Through activation, stabilization, and assistance in the correct conformation of client proteins, Hsp90 plays a key role in oncogenesis.[33] Inhibition of Hsp90 causes the breakdown of its client proteins through the ubiquitin-proteasome pathway.[33] Earlier studies of HSP inhibitors demonstrated only modest therapeutic effects as single agents.[31] Liver toxicity was noted as a limitation of the early molecules studied, as well as suboptimal

THE AMERICAN JOURNAL OF MANAGED CARE
Evidence-Based Oncology

Date Updated	Company	Product	Mechanism of Action	Indications	Stage	Licensee/Partner(s)	PDUFA Date
N/A	Merck Serono S.A. (The Merck Group)	Atacicept (TACI-Ig)	Recombinant Fusion Protein	Multiple myeloma	Preclinical trials	N/A	N/A
05/03/2012	Novartis Pharmaceuticals	NVP-AUY922	Hsp90 Inhibitor	Relapsed or refractory multiple myeloma	Phase I/II	N/A	N/A
04/02/2012	Onyx Pharmaceuticals	Carfilzomib	Proteasome Inhibitor	Relapsed or refractory multiple myeloma	Phase III	N/A	N/A
05/01/2012	Cephalon	Delanzomib (CEP-18770)	Proteasome Inhibitor	Relapsed or refractory multiple myeloma	Phase I/II	Teva Pharmaceutical Industries Ltd	N/A
11/11/2011	Seattle Genetics	Dacetuzumab (SGN-40)	Monoclonal Antibody	Relapsed or refractory multiple myeloma	Phase I	Genentech (Hoffman-LaRoche)	N/A
05/03/2012	Bristol-Myers Squibb Co.	Elotuzumab (BMS-901608; HuLuc63)	Monoclonal Antibody	Relapsed or refractory multiple myeloma	Phase III	Abbott Biotherapeutics Corp	N/A
04/09/2012	Kyowa Hakko Kirin Pharma	KW-2478	Hsp90 Inhibitor	In combination with bortezomib to treat patients with relapsed and/or refractory multiple myeloma.	Phase I/II	Kyowa Hakko Kirin Company, Ltd	N/A
06/22/2010	Nereus Pharmaceuticals	Marizomib (NPI-0052)	Proteasome Inhibitor	Relapsed or relapsed/ refractory multiple myeloma.	Phase I	N/A	N/A
04/27/2012	Millennium Pharmaceuticals (Takeda Pharmaceuticals)	MLN9708	Proteasome Inhibitor	Newly diagnosed or relapsed/refractory multiple myeloma	Phase I/II	N/A	N/A
11/23/2011	Novartis Pharmaceuticals	Panobinostat (LBH-589)	Deacetylase Inhibitor	Relapsed and bortezomib-refractory multiple myeloma	Phase I/II	N/A	N/A
02/29/2012	Keryx/AOI Biopharmaceuticals	Perifosine (KRX-0401)	Akt Inhibitor	Relapsed and bortezomib-refractory multiple myeloma	Phase III	Dana-Farber Cancer Institute	N/A
04/11/2012	Celgene Corporation	Pomalidomide (CC-4047)	Immunomodulator	Refractory or relapsed and refractory multiple myeloma	Phase III	N/A	N/A
08/11/2011	Celgene Corporation	Romidepsin (FK228; FR901228)	Deacetylase Inhibitor	Relapsed or refractory multiple myeloma	Phase I/II	Janssen-Cilag Ltd; Peter MacCallum Cancer Centre, Australia	N/A
04/20/2012	Janssen Pharmaceutical K.K. (Johnson & Johnson)	Siltuximab (CNTO-328)	Monoclonal Antibody	In combination with bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma	Phase I	N/A	N/A
04/16/2012	Threshold Pharmaceuticals	TH-302	DNA Alkylating Agent	Relapsed/refractory multiple myeloma	Phase I/II	N/A	N/A
12/28/2011	Merck & Co.	Vorinostat (SAHA)	Deacetylase Inhibitor	Relapsed or refractory multiple myeloma	Phase II	Hackensack Univ. Medical Center	N/A

N/A indicates not available; PDUFA, Prescription Drug User Fee Act.

degradation of client proteins, possibly due to suboptimal dosing or schedules. Additionally, a resistance mechanism was observed with tanespimycin mediated through P-glycoprotein efflux.[31]

AUY922

Recent in vitro and in vivo studies utilizing AUY922, a novel Hsp90 inhibitor, in combination with either panobinostat, vorinostat, melphalan, or doxorubicin showed primarily synergistic effects.[32] Of particular note was the ability of the investigators to show that the best result was seen when the drug was continued for another 48 hours after 24 hours of the combination regimens.[32] While resistance was seen in 1 MM cell line and several primary cell samples from patients when AUY922 was used only as monotherapy, the remarkable results of the combination regimens pave the way for future clinical trials and show great promise.[32]

KW-2478

KW-2478 is also an Hsp90 inhibitor that has been identified as a viable therapeutic moiety and has been studied to further characterize its properties and place as a suitable therapeutic agent. In animal studies using the drug, there were no identified cases of hepatotoxicity, as seen with other structural analogues.[31,33] Additionally, the drug had a favorable pharmacokinetic profile, was found to be soluble in saline, and showed no metabolism through the CYP3A4 pathway.[33] Additional studies are under way in human subjects, with KW-2478 being used in combination with bortezomib.[34]

Alkylating Agent—TH-302

TH-302 is a modified prodrug derived from ifosfamide and belongs to the alkylating agent drug class.[35] MM cells can be found together in extreme oxygen-deprived environments in the bone marrow. Hypoxic environments are seldom found in healthy tissues, making them a viable target for tumor-specific therapy. TH-302 potency was enhanced 10-fold through chemical modification and is uniquely activated under hypoxic conditions. It causes G_0/G_1 cell-cycle arrest by down-regulating cyclinD 1/2/3, CDK 4/6, p21clp-1, p27klp-1, and pRb expression in in vitro studies.[35] This translates into the apoptosis of MM cells by up-regulating the cleaved proapoptotic caspase-3, -8, -9, and poly ADP-ribose polymerase while having no significant effects under normal oxygen conditions. Further studies in mice models demonstrated apoptosis within the bone marrow microenvironment, including other markers of activity such as decreases in paraprotein secretion and decreases in microvesical density. Preclinical trials examined TH-302 monotherapy and in combination with gemcitabine, pemetrexed, doxorubicin, and docetaxel. As monotherapy, TH-302 has demonstrated dose-dependent effects and low toxicity under normal oxygen conditions, warranting further study in human trials.[35]

Conclusion

While MM has remained an incurable disease, new therapeutic agents have provided viable treatment options with encouraging results despite the fact that all patients relapse at some point. Research

and development surrounding MM targets remains very active, with a number of drugs under evaluation for the treatment of MM. However, only a few of these drugs are currently in Phase III trials, and results of some recent trials have been disappointing. The most promising agents emerging include the so-called "second generation" proteasome inhibitors, with some that are orally active and have better pharmacokinetic profiles, more potent therapeutic effects, and the ability to overcome resistance. Additional treatment options that may become available as they are undergoing Phase III trials are a more potent IMiD (pomalidomide),[7] a new mAb that is directed at cell surface glycoprotein CS1 (elotuzumab),[26] and an orally administered Akt inhibitor (perifosine).[30] Other therapeutic agents are in the earlier stages of development, but a large percentage of studies have demonstrated that further trials are warranted. Despite these new agents on the horizon, MM needs to remain a target for new drug development to help overcome the high relapse rates and refractory disease associated with this cancer. **EBO**

Author Affiliations: Our Lady of the Lake Regional Medical Center (MMM), Baton Rouge, LA; and University of Louisiana at Monroe College of Pharmacy—Baton Rouge Campus (BLM), Baton Rouge, LA.

Funding Source: None.

Author Disclosures: Dr M. M. Mohundro reports receiving payment for involvement in the preparation of this manuscript. Dr B. L. Mohundro reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (BLM); acquisition of data (BLM); analysis and interpretation of data (MMM, BLM); drafting of the manuscript (MMM, BLM); and critical revision of the manuscript for important intellectual content (MMM, BLM).

References

1. Myeloma Snapshot. http://cancer.gov/aboutnci/servingpeople/snapshots/myeloma.pdf. Accessed March 10, 2012.

2. Multiple myeloma. American Cancer Society website. http://www.cancer.org/Cancer/MultipleMyeloma/DetailedGuide/multiple-myeloma-key-statistics. Accessed March 10, 2012.

3. Nau KC, Lewis WD. Multiple myeloma: diagnosis and treatment. *Am Fam Physician*. 2008;78(7):853-859.

4. What is multiple myeloma? http://www.themmrf.org/living-with-multiple-myeloma/newly-diagnosed-patients/what-is-multiple-myeloma/definition.html. Accessed March 10, 2012.

5. Ferri FF. *Ferri's Clinical Advisor 2012*. Philadelphia: Elsevier Mosby; 2012:661-662.

6. Lacy MQ. New immunomodulatory drugs in myeloma. *Curr Hematol Malig Rep*. 2011;6:120-125.

7. Pomalidomide and multiple myeloma. Clinical Trials.gov website. http://clinicaltrials.gov/ct2/results?term=pomalidomide&recr=&rslt=&type=&cond=myeloma&intr=&outc=&lead=&spons=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&gndr=&rcv_s=&rcv_e=&lup_s=&lup_e=. Accessed March 12, 2012.

8. Hideshima T, Richardson PG, Anderson KC. Mechanism of action of proteasome inhibitors and deacetylase inhibitors and the biological basis of synergy in multiple myeloma. *Mol Cancer Ther.* 2011;10(11):2034-2042.

9. Mujtaba T, Dou QP. Advances in the understanding of mechanisms and therapeutic use of bortezomib. *Discov Med*. 2011;12(67):471-480.

10. Chauhan D, Singh AV, Ciccarelli B, Richardson PG, Palladino MA, Anderson KC. Combination of novel proteasome inhibitor NPI-0052 and lenalidomide trigger in vitro and in vivo synergistic cytotoxicity in multiple myeloma [published online ahead of print November 13, 2009]. *Blood*. 2010;115(4):834-845.

11. Jain S, Diefenbach C, Zain J, O'Connor OA. Emerging role of carfilzomib in treatment of relapsed and refractory lymphoid neoplasms and multiple myeloma [published online ahead of print April 4, 2011]. *Core Evid*. 2011;6:43-57.

12. Carfilzomib. Onyx Pharmaceuticals website. http://www.onyx.com/clinical-development/carfilzomib. Accessed March 12, 2012.

13. Kupperman E, Lee EC, Cao Y, et al. Evaluation of the proteasome inhibitor MLN9708 in preclinical models of human cancer [published correction appears in: *Cancer Res*. 2010;70(9):3853] [published online ahead of print February 16, 2010]. *Cancer Res*. 2010;70(5):1970-1080.

14. MLN9708 and myeloma. ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/results?term=mln9708+multiple. Accessed March 12, 2012.

15. Phase 1 clinical trial of NPI-0052 in patients with relapsed or relapsed/refractory multiple myeloma. ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT00461045?term=npi0052+myeloma&rank=1. Accessed March 12, 2012.

16. Sanchez E, Li M, Steinberg JA, et al. The proteasome inhibitor CEP-18770 enhances the anti-myeloma activity of bortezomib and melphalan [published online ahead of print December 1, 2009]. *Br J Haematol*. 2010;148(4):569-581.

17. CEP18770 and myeloma. http://clinicaltrials.gov/ct2/results?term=myeloma+CEP18770. Accessed March 12, 2012.

18. Harrison SJ, Quach H, Link E, et al. A high rate of durable responses with romidepsin, bortezomib, and dexamethasone in relapsed or refractory multiple myeloma [published online ahead of print September 12, 2011]. *Blood*. 2011;118(24):6274-6283.

19. Romidepsin and myeloma. http://clinicaltrials.gov/ct2/results?term=romidepsin+and+myeloma. Accessed March 12, 2012.

20. Ocio EM, Vilanova D, Atadja P, et al. In vitro and in vivo rationale for the triple combination of panobinostat (LBH589) and dexamethasone with either bortezomib or lenalidomide in multiple myeloma [published online ahead of print November 30, 2009]. *Haematologica*. 2010;95(5):794-803.

21. Panobinostat and myeloma. ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/results?term=panobinostat+myeloma. Accessed March 12, 2012.

22. Chustecka Z. Vorinostat shows activity as salvage in multiple myeloma. http://www.medscape.com/viewarticle/755437. Accessed March 12, 2012.

23. Yang J, Yi Q. Therapeutic monoclonal antibodies for multiple myeloma: an update and future perspectives. *Am J Blood Res*. 2011;1(1):22-33.

24. Hunsucker SA, Magarotto V, Kuhn DJ, et al. Blockade of interleukin-6 signalling with siltuximab enhances melphalan cytotoxicity in preclinical models of multiple myeloma [published online ahead of print January 17, 2011]. *Br J Haematol*. 2011;152(5):579-592.

25. A phase 3 study of siltuximab or placebo in combination with velcade and dexamethasone in patients with relapsed or refractory multiple myeloma. http://clinicaltrials.gov/ct2/archive/NCT01266811. Accessed March 12, 2012.

26. Jakubowiak AJ, Benson DM, Bensinger W, et al. Phase I trial of anti-CS1 monoclonal antibody elotuzumab in combination with bortezomib in the treatment of relapsed/refractory multiple myeloma [published online ahead of print January 30, 2012]. *J Clin Oncol*.

27. Hussein M, Berenson JR, Niesvizky R, et al. A phase I multidose study of dacetuzumab (SGN-40; humanized anti-CD40 monoclonal antibody) in patients with multiple myeloma [published online ahead of print February 4, 2010]. *Haematologica*. 2010;95(5):845-848.

28. Rossi JF, Moreaux J, Hose D, et al. Atacicept in relapsed/refractory multiple myeloma or active Waldenström's macroglobulinemia: a phase I study. *Br J Cancer.* 2009;101(7):1051-1058.

29. Hideshima T, Catley L, Yasui H, et al. Perifosine, an oral bioactive novel alkylphospholipid, inhibits Akt and induces in vitro and in vivo cytotoxicity in human multiple myeloma cells [published online ahead of print January 17, 2006]. *Blood*. 2006;107(10):4053-4062.

30. Perifosine and myeloma. http://clinicaltrials.gov/ct2/results?term=perifosine+myeloma. Accessed March 12, 2012.

31. Neckers L, Workman P. Hsp90 molecular chaperone inhibitors: are we there yet? *Clin Cancer Res*. 2012;18(1):64-76.

32. Kaiser M, Lamottke B, Mieth M, et al. Synergistic action of the novel HSP90 inhibitor NVP-AUY922 with histone deacetylase inhibitors, melphalan, or doxorubicin in multiple myeloma [published online ahead of print December 17, 2009]. *Eur J Haematol*. 2010;84(4):337-344.

33. Nakashima T, Ishii T, Tagaya H, et al. New molecular and biological mechanism of antitumor activities of KW-2478, a novel nonansamycin heat shock protein 90 inhibitor, in multiple myeloma cells [published online ahead of print April 20, 2010]. *Clin Cancer Res*. 2010;16(10):2792-2802.

34. A study of kw-2478 in combination with bortezomib in subjects with relapsed and/or refractory multiple myeloma. ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT01063907?term=kw2478+myeloma&rank=1. Accessed March 12, 2012.

35. Hu J, Handisides DR, Van Valckenborgh E, et al. Targeting the multiple myeloma hypoxic niche with TH-302, a hypoxia-activated prodrug [published online ahead of print June 7, 2010]. *Blood*. 2010;116(9):1524-1527.

Oncology Hit Hard by SGR Debacle

How Do We Permanently Fix a Flawed System?

Interview With Allen S. Lichter, MD, Chief Executive Officer, American Society of Clinical Oncology

Allen S. Lichter, MD, Chief Executive Officer, American Society of Clinical Oncology (ASCO), spoke with Evidence-Based Oncology on the sustainable growth rate (SGR). Created to compute cuts in physician reimbursements, the SGR was established to contribute to long-term savings from healthcare providers. The SGR formula results in progressively larger reductions each year in fees that Medicare pays its physician providers.

In this interview, Dr Lichter address suggested proposals to fix the SGR, such as the use of leftover war funds and ASCO's Quality Oncology Practice Initiative (QOPI), which is used as a tool to measure quality and performance as part of the basis for physician payment reform.

EBO: **How do you think Congress will deal with the proposal to use leftover war funds to repeal the SGR?**

Dr Lichter: There are many proposals floating around about how one might deal with the SGR. We see information that suggests that there are enough funds that can be recovered from the winding down of military conflicts to cover the SGR fix, and permanently erase it. We certainly hope that is the case. The problem with patches is 2-fold. Number 1, it is the classic kick-the-can-down-the-road. Every time the SGR is patched, when that patch runs out, the cost of the permanent fix has gone up because the additional costs simply accumulate. In the middle of the last decade the cost of replacing or covering the SGR formula was $49 billion. It is now close to $300 billion. If it's patched for another year or two it's going to start to get into the $350 and $400 billion range. Eventually, it could become such a costly item that it can almost never be fixed. The second thing about a patch is that it creates uncertainty in the medical community.

THE AMERICAN JOURNAL OF MANAGED CARE

Physicians need to make plans. They may need to buy equipment, such as new technology, or electronic health records. They may need to hire staff or expand their offices, or do a whole variety of things related to caring for their patients. When one does not know whether payments from Medicare are going to be suspended again, as they have been several times in the past couple of years, and cash flow into the practice is going to stop, and so on and so forth, physicians are extremely reluctant to make long-term plans for running their practices appropriately, and that is extremely detrimental to the practice of medicine and to the care of patients. So, we hope that Congress can create a permanent fix and allow this flawed system, which everybody agrees has to go, to go. Let's get it done and let's get it over with.

EBO: **If it were up to you, how would you go about scrapping SGR?**

Dr Lichter: That's the $64,000 question, isn't it? If people knew for sure what to replace it with, it's possible that it would have been replaced a long time ago. I can tell you my own feeling is that no one is smart enough to sit down and write a solution that when applied in the field across hundreds of thousands of physicians and millions of patients will work perfectly. Our sense is that we have the Center for Medicare and Medicaid Innovation, and we need to come up with multiple programs and run a series of well-constructed pilot tests, and then bring the things that work forward and incorporate them, and take the things that don't work and either fix them or throw them out. To some extent this is what CMS [Center for Medicare & Medicaid Services] did as they moved toward ACOs [accountable care organizations]. They ran pilots with large physician group practices managing a population of patients and sharing cost savings based on their ability to reduce the rate of rise of healthcare costs in this population. They figured out what worked and how to do it and that allowed them to move more confidently into a large-scale rollout of ACOs. The same thing needs to apply here, we need to run the pilots that allow us to say how should we use bundled payments, how should we use episode-based care, how might various capitation systems work, what will be the impact of ACOs, and how does that get folded in? Our sense is to allow physicians the certainty of knowing that the SGR is done, and allow us to work with CMS in a series of well-crafted pilot projects, and build the next generation of physician reimbursement strategies based on good solid data.


Allen S. Lichter, MD

EBO: **ASCO has proposed implementing its QOPI as a solution. What came of that initiative?**

Dr Lichter: We are talking broadly to people on the Hill and inside CMS about the concepts surrounding quality and performance measurement as part of the basis for physician payment reform. I say that in the following way, if one assumes that physician payment reform needs to be coupled with appropriate cost savings inside the Medicare system so the system doesn't completely go bankrupt, then we must know if we're going to be making those types of choices, that the quality of care is not being compromised. Just as we would want to monitor whether too much is being done and funds are being wasted, we need to monitor whether too little is being done and care is being inappropriately withheld, and that's done through a robust quality monitoring system that's accurate, that's real time, that's validated, and that physicians believe in. Not just in oncology, this really applies across medicine. To monitor oncology quality is very complex. Cancer is a hundred different diseases, and each of those diseases begins to parse out into dozens of subtypes of disease based on the stage of disease, and the age of the patient, and the genomic profile of the cancer. You can't have a handful of performance measures in oncology and monitor oncology quality. We believe that ASCO and the profession need to be at the center of this and want to work with Congress and with CMS to couple our experience and expertise and quality monitoring, and to make sure that any solution we put into place not only is cost-effective, but allows patients to receive the very highest quality care.

EBO: **I would think oncology would be particularly impacted of almost all of the other specialties or therapeutic areas.**

Dr Lichter: It is in some respects because of multiplicity of diseases, and subsets of diseases, and subsubsets of diseases. It is in some respects the most complicated area for quality monitoring that there is, and we know it can be done. Our QOPI now has over 100 measures. We are adding more, and based on that foundation we can build a quality monitoring system that is extremely robust. We also have the opportunity to build off the incentives that the government has put forward for physicians to move onto electronic health records, and the ability for us to craft a quality monitoring system that's seamless and works behind the scenes electronically, and supports physicians making the very best decisions on behalf of their patients, and allows patients to have access to information that helps them make informed choices. All of these things are possible if we can work together toward a common goal.

EBO: **Under the SGR formula, physicians almost seem forced to participate in the fee-for-service system to avoid losing money. This seems to counteract the financial incentives offered to physicians who choose to participate in streamlining their services under health reform. What are your thoughts?**

Dr Lichter: The current Medicare payment methodology is fee-for-service, and fee-for-service is a system that is very common, almost universal, for how professionals build their service. Attorneys charge fees, architects charge fees, accountants charge fees, and physicians charge fees. What has happened over time is that the number of things physicians can do and the number of patients and the number of medical conditions that we can now affect has just grown and grown and grown. If the amount of funding to pay the fees is finite and to some extent the number of things we can do keeps growing and growing, then the fee for each unit of service needs to be cut. That's essentially, in very broad brush strokes, how the SGR dug the hole that we're in. It's unlikely that there's a modification of a classic fee-for-service system that will work. We get into this situation where physicians do more and more and keep running faster and faster to stay in place, and that doesn't work well. If you try to control costs inside a fee-for-service system the examples are numerous that, in fact, physicians or hospitals or healthcare organizations actually lose money. You do fewer things, you build fewer fees, and funding goes down. So we have to create a system where the ability to practice high-quality care that is cost-effective doesn't put you out of business, but in fact is rewarded with the appropriate incentives.

The other thing that happens in an SGR system, of course, is that it is 1 figure for the entire country. So, you lump physicians who are working very hard and successfully at cost control in with groups of providers who are less skilled at that. So, the people who are making adjustments are not getting rewarded. They're getting hammered just as physicians and providers who are doing less well. A system needs to be created where there is some level of individual identification and individual responsibility. Say, if you're doing well and achieving appropriate goals, we're going to recognize you as an individual or healthcare system, or a practice, and single you out and not group you in with 750,000 other physicians. If it were easy it would have been done. You cannot talk to a single person involved in this in any way who says this is a good system and keep it going. Nobody wants to continue this. It's just a question of finding the will to fix it, the funds to abolish it, and to have the plans to study and pilot and experiment as we find the right solution. It would be a shame to throw out the SGR system and put in its place something that turns out to be just as bad or worse. We can't afford to make another serious miscalculation this time around. We have to find the right path here.

EBO: **Looking at quality of care in the realm of the broken Medicare payment system for oncology patients, it seems like this would be a really rough road to go down. Can you talk to the impact on patients?**

Dr Lichter: Certainly if the SGR is not fixed and the cuts go forward, 27.5% now and you know, next year 30% or more, and so on and so forth, it is not thinkable as to the impact that that would be in an oncology practice. Approximately 60% to 65% of all cancer cases occur in patients older than 65 years. Medicare is the single largest provider of oncology care in the country. If reimbursement rates were pushed off the side of a mountain because we couldn't solve the SGR, it would devastate oncology care. I don't know what would happen because certainly practices could not reasonably afford to provide that care.

We are extremely willing and anxious to be part of the solution to this problem. We are in this together, and want to work together not only as an oncology field, but as a member of the larger community, of medicine and specialty societies, to solve this problem. I am certain it can be done. We just need to roll up our sleeves and do it. **EBO**

Author Affiliation: American Society of Clinical Oncology, Alexandria, VA.

Funding Source: None.

Author Disclosure: The author reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

THE CONFERA GROUP PRESENTS

Access to Innovative Cancer Therapies

7th Annual Oncology Economics Forum

June 19 & 20, 2012

Hyatt Regency Philadelphia
at Penn's Landing

Philadelphia, PA

The *Access to Innovative Cancer Therapies in 2012 - 7th Annual Oncology Economics Forum* will bring together top experts within the oncology arena to present the latest perspectives regarding the most critical issues surrounding payer coverage, reimbursement and pricing issues, and policy decisions impacting the oncology marketplace.

Gain valuable insight regarding:

- Healthcare Reform Initiatives Impacting Cancer Care
- ACOs and Oncology Medical Home: Examining New Delivery Care Models
- New Trends Regarding Patient Access to Oncology Therapies
- Predictions for Payer – Provider Pathway Initiatives
- Commercial Payer Coverage Decision Criteria & the Outlook Regarding Emerging Payer Models
- Oncology Access and Coverage Regarding Medicare Payments
- Key Issues that will Impact Pricing and Reimbursement Decisions in the Near Future
- Evolving Definitions and Perceptions of "Value Proposition" in Oncology
- Global Reimbursement & Access Trends in Oncology and Potential Implications for the U.S.

ONCOLOGY FORUM

For more information and to register for this conference:

Visit www.conferagroup.com
Call 704.849.6934

ACCESS.
ENROLLMENT.
INFORMATION.

Now available in one place: **Everywhere.**

Announcing our new health care professional portal for *Dendreon ON Call*—featuring electronic patient enrollment and e-services—for fast, efficient access to enrollment updates, benefits verification, reminders, and much more. *Dendreon ON Call* is your source for comprehensive patient and product support and reimbursement expertise.

Visit us today at www.PROVENGEReimbursement.com or call *Dendreon ON Call* at 1-877-336-3736.

Fast • Accurate • Secure • Open 24/7 Online

Dendreon
Targeting Cancer, Transforming Lives®

PROVENGE®
(sipuleucel-T)