Bridging the gap between payer and provider perspectives

THE AMERICAN JOURNAL OF MANAGED CARE

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Volume 18
Special Issue 1

Evidence-Based Oncology

Commentary

Trying Something New: Episode Payments for Cancer Therapy

Radical Changes in Payment Incentives and Elimination of Low-Value Care

Lee N. Newcomer, MD, MHA

My recent personal experiences illustrate the current issues for healthcare delivery. Last spring, a driver behind me was blinded by the early morning sun, and she did not see that I had stopped at a stop sign. It only took 4 hours after the rear-end collision for me to develop the aches and pains of a minor whiplash injury. My internist was booked, so I accepted an alternative appointment with a new physician who was 1 year out of residency. My exam was normal except for a neck spasm. My new physician wrote a prescription for some pain medication and a muscle relaxant. Then he began scheduling a magnetic resonance imaging (MRI) scan of the neck.

"Give me a moment," I asked. "Isn't my exam normal?"

"Yes," he said.

(continued on page SP5)

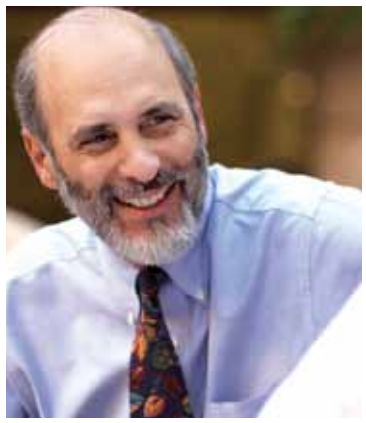
Clinician Interview

Unraveling the Complexity of Drug Shortages

Grim Reality Is a Bitter Pill to Swallow

Interview with ASCO President Michael P. Link, MD, Lydia J. Lee Professor of Pediatric Hematology/Oncology, Stanford University School of Medicine, and Director of the Bass Center for Cancer and Blood Diseases at the Lucile Salter Packard Children's Hospital.

The last thing an oncologist wants to hear is that a medication he or she has prescribed is unavailable. But the reality is that drug shortages, while not new, have reached a crisis level. The medications in short supply run across multiple specialties, but the impact is most prevalent—and devastating—in oncology.



Michael P. Link, MD

The American Cancer Society reports that patients with lung, breast, ovarian, and rarer forms of cancer face the biggest health risk when medications like paclitaxel, fluorouracil, doxorubicin, and bleomycin are scarce. An alternate drug may not work as well and there may be increased side effects.

A recent statistic points to the magnitude of the problem: an IMS Institute for Healthcare Informatics analysis found that 550,000 cancer patients were impacted by the drug shortage as of the year ended June 30, 2011.

One of the more prominent leaders working toward a solution is Dr Michael Link, president of The American Society of Clinical Oncology (ASCO). This past summer, Dr Link addressed the drug shortage problem at a Capitol Hill briefing. ASCO's influence also was evident when, on November 30, 2011, the US House of Representatives Oversight and Government Reform Subcommittee on Health Care, District of Columbia, Census and the National Archives held a hearing on drug shortages. Testimony ranged from declaring the situation a "massive national emergency" to calling on the FDA to

(continued on page SP8)

Clinician Interview

Putting Value Into Practice

Insights Into Value-Based Insurance Design in Oncology

The University of Michigan (U-M) Center for Value-Based Insurance Design (V-BID) has been gaining momentum since its 2005 launch, guiding efforts to support the development, implementation, and evaluation of innovative health benefit designs balancing cost and quality. Since that time, numerous private and public employers, unions, and business coalitions nationwide have implemented value-based insurance design

A. Mark Fendrick, MD

approaches. V-BID has been recognized as an important public policy measure for balancing costs and quality in healthcare at the local, state, and federal level. V-BID was incorporated into federal health reform law—Section 2713 (c) of the Patient Protection and Affordable Care Act, which passed in 2010.

The foundation of value-based insurance design is rooted in removing barriers to essential, high-value health services. V-BID programs improve health outcomes at any level of healthcare expenditure. Studies show that when barriers are reduced, significant increases in patient compliance with recommended treatments and potential cost savings result.

In the following interview, A. Mark Fendrick, MD, one of 3 co-founders of the U-M

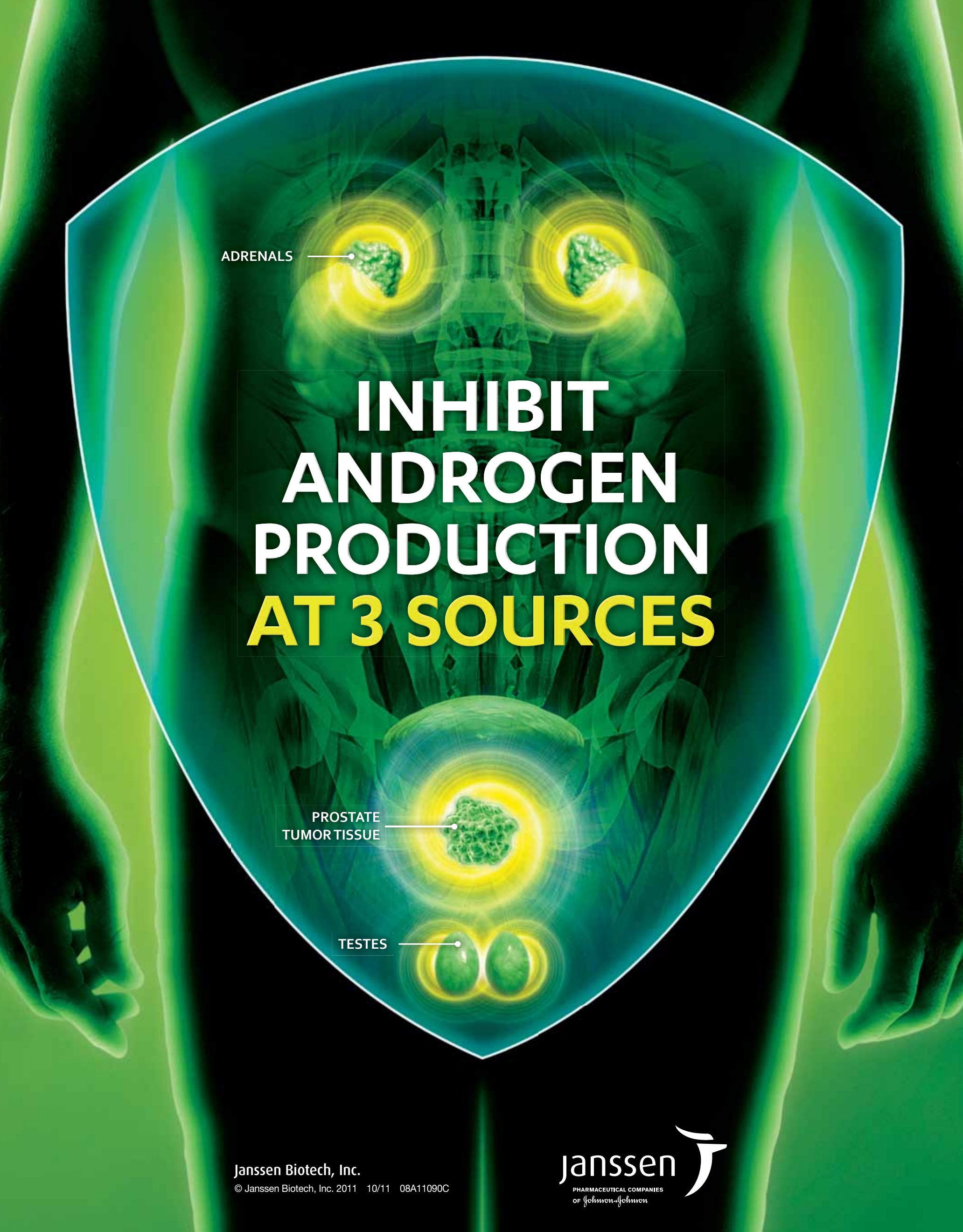
(continued on page SP11)

Also in this issue...

AJMC TV

Mark Zitter, Founder and CEO, The Zitter Group, talks about his newest business venture that provides end-of-life cancer patients with a telephone counseling service.

Dawn Holcombe, president of DGH Consulting and executive director of the Connecticut Oncology Association, discusses collaborative trends between payers and providers in an oncology setting.



INHIBIT ANDROGEN PRODUCTION AT 3 SOURCES

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

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THE AMERICAN JOURNAL OF MANAGED CARE

In This Issue SP3

THE AMERICAN JOURNAL OF MANAGED CARE

The ability to deliver affordable cancer care is at a crossroads. A volatile mixture of demographics (eg, aging and expanding populations), rapid development of new technologies (eg, drugs and surgery), the delicate balance between drug side effects and overall survival ratio, and increasing healthcare expenditure is driving costs higher.

Although price controls are a readily available means to control cost in oncology and in other areas of medicine, there is an important and vulnerable link between pricing and innovation. Thus, there is increasing interest in value-based pricing that would reward and incentivize development of drugs that substantially improve outcomes, but not subsidize development of me-too or marginally effective new treatments. Of course, the framework for balancing support for innovation, cost control, and continued evidence development is the subject of active debate.

With the oncology healthcare landscape changing every day, payers have difficulty tracking and managing the expenditures in oncology, and providers struggle to understand the burgeoning regulatory issues and narrow indications that limit their use in practice.

To help facilitate understanding between payers and providers in oncology, *The American Journal of Managed Care* is publishing *Evidence-Based Oncology*, a publication that presents clinical, pharmacoeconomic, and regulatory information to help inform individual decisions — by providers, payers, and policy makers — with the goal of improving efficiency and outcomes in cancer care.

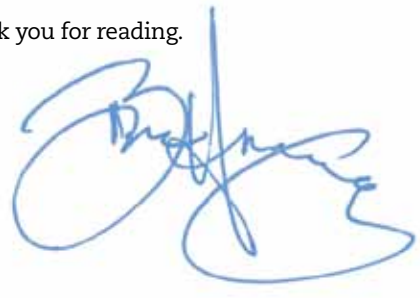
This publication will prove to be one of your "must-reads" right away, as our mission is to bring you the most relevant, timely, and thought-provoking content in your field. In each issue, you will find biting-edge Clinician Interviews with key opinion leaders. Next, our expert authors provide informative Commentaries to kick off the discussion, bring out salient points, and raise questions. Finally, our Best Practice section provides you with a bird's-eye view of clinical pathways adopted by the finest cancer centers in the country.

Additionally, we offer Pipeline Reports focusing on specific tumor types to keep you informed on oncology drugs moving through clinical trials. "Latest in Literature" reviews the most recent evidence-based literature and examines the thrust of the findings to provide the important information you need to know in quick-to-read summaries. "Drug Profiles" highlights specific products to help oncology providers better understand both their mechanisms of action and the economic implications of their use.

We will also regularly provide the latest information on biomarkers, health information technology, and health policy, and how changes in these fields are impacting evidence-based healthcare in oncology.

Utilizing best practices and improving efficiency and outcomes in cancer care—and keeping an open mind as to how best to accomplish these goals—is the reason *Evidence-Based Oncology* is arriving at your door.

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.

MH

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Episode Payments for Cancer Therapy
(continued from cover)

"Do you really think I have any pathology in my neck based on the history and exam?"

"No," he said.

He then explained that he was being cautious; he did not want to miss anything. I told him what I do for a living and explained that I was more than willing to take the meds, rest, and wait to see whether I improved. If I did not get better, I said, I would return for the MRI. We developed a plan for follow-up and shook hands on the agreement.

As I left, he turned the tables on me: "You do realize," he said, "that your insurers pay me more to do the MRI than to have this discussion."

Misaligned payment incentives for technology and inadequate payment for discussion and planning encourage physicians to do more rather than less. Even the overrated threat of malpractice is illustrated in this example. In addition, this young physician did not have a forum in which to compare results and costs with his peers, so any quality improvement was left to his ingenuity.

The same issues are exaggerated in medical oncology in which an old payment system has created strong and perverse incentives for care. Medical oncologists evaluate patients with cancer to determine the extent of the disease and then recommend therapy. Treatment options for cancer include surgery, radiation therapy, chemotherapy, or combinations of those 3. If chemotherapy is recommended, the medical oncologist administers those drugs in his office. Medical oncologists purchase chemotherapy drugs at wholesale prices from manufacturers and then bill the payer at retail prices. This payment system originated in the 1960s when few chemotherapy drugs were available and their costs were minimal. However, as more drugs were discovered and as the cost of those drugs increased, a major shift occurred in medical oncology economics. Today, the profit margin from these drug sales accounts for approximately 65% of a medical oncology practice's income. These profits are essential to cover the overhead of the community oncology office.

The current system does have benefits. The administrative overhead of a dedicated oncology clinic is usually much lower than alternatives in outpatient hospital-based clinics, so they can offer these services for a lower cost. Unpublished UnitedHealthcare (UHC) data show that private offices also use fewer ancillary services for a cancer episode compared with hospital-based outpatient clinics. Combining those 2 factors—cost and use—has a startling impact. At UHC, the total cost of care for a patient actively on chemotherapy is approximately 2 times higher if the patient is treated in a hospital outpatient clinic than if that patient is treated in a community oncology office.

Unfortunately, there were excesses when profit margins were high. Medicare responded to this problem by lowering chemotherapy reimbursement levels to approximate cost. Using a calculation called Average Sales Price, the federal government pays a 6% margin on its calculated acquisition cost for each drug. But as with any new payment system, unintended consequences quickly emerged.

Even with a fixed margin, the net profit on an expensive drug is higher than that of a low-cost drug. Many generic drugs yielded margins that measured in the pennies whereas new, branded products could generate hundreds of dollars by using the same 6% margin. Not surprisingly, physicians increased the use of expensive chemotherapy drugs. Using Medicare data, Harvard researchers showed that a medical oncologist would prescribe the most expensive regimen when there were multiple choices of therapy.[1] This incentive has significant implications for total cost. The study noted that each dollar of incremental profit for the medical practice cost Medicare an additional $23 for drug expenditures. With the Medicare decrease in payment, practices started shifting patients to hospital facilities for treatment or shifting their losses to private payers. Private insurers began experiencing inflation trends of 15% annually for cancer care after the Medicare payment change.

A new payment system is needed. When UHC began developing a new pilot payment program to correct the existing problems, it had 3 objectives: (1) separate the oncologist's income from drug sales, (2) retain the medical oncologists' personal incomes at current levels, and (3) create an objective performance measurement system that becomes the basis for future payment increases. The pilot started with 5 volunteer medical oncology groups. Each medical group agreed to 2 key requirements to participate. They chose a standard chemotherapy regimen for each of 19 clinical presentations in breast, colon, and lung cancer, and they agreed to participate in a joint performance review with the other participating oncology groups.

Once the groups selected their regimens, UHC calculated the profit margin amount of money each group would make on drug profits for each of the 19 clinical presentations by using the difference between the group's current fee schedule and the drug costs. A case management fee was added to this amount, and the amount became the patient care episode fee. This new episode fee would be paid on the first day when the patient would receive care from the group. Drugs were reimbursed at cost. The medical group was free to change their drug regimens at any time, but the episode payment would not change. Office visits, chemotherapy administration codes, and other ancillary services—like laboratory tests—were paid on a fee-for-service basis. Adjuvant treatment episode fees were single payments that covered the time period of the adjuvant regimen. Episode fees for patients with metastatic disease would renew every 4 months, even if the patient elected not to receive additional chemotherapy. UHC is gathering data for clinical and cost profiles of each clinical category. These data are shared openly with all 5 groups. Measurements include complication rates, relapse rates, pain control admissions, and total medical costs. Because each group is treating its patients with a consistent regimen, the pilot creates a comparative effectiveness analysis that allows all of us to identify best practices. If and when a best practice is identified, it is UHC's expectation that groups will transition care to that practice.

This novel approach accomplishes several important goals. Drug selection is based on best practices rather than income maximization. Oncologists will be able to compare their performance with that of other groups and adopt best practices. UHC anticipates that use of medications with minimal responses will diminish, because physicians will not see any improvement in their clinical performance as they compare data. This program does not penalize the oncologist for participating, because current income is preserved. This method does not address the new drug pricing by pharmaceutical manufacturers. Neither UHC nor the physician community can negotiate effectively when new, single-source drugs are approved for use, because there are no alternatives. In addition, price increases on existing drugs from manufacturers are not addressed.

A second personal experience illustrates why something must be done differently. My son's roommate—a nursing student at the University of Nevada—called me last weekend; she needed help diagnosing a rash for one of her friends. The young nurse was convinced it was the target rash of Lyme disease. Using her cell phone camera, she sent me a photo that could have been used as an illustration in a medical textbook. I gave her my opinion and told her that her friend needed medical care that day. That was when I found out that the patient did not have medical insurance. Although the friend had graduated with a college degree, she was subsisting on 3 different part-time, minimum-wage jobs; none of the jobs offered insurance, and she could not afford the premium if she was going to pay rent, buy food, and put gasoline in her car.

Healthcare coverage is simply unaffordable for too many people. It will only become affordable with radical changes in payment incentives and the elimination of care that does not really matter. The UHC pilot may help, and it may not; it is an experiment. My wish is to see hundreds of experiments in the next 5 years. Only through change are we going to find solutions that work. **EBO**

"A new payment system is needed. When UHC began developing a new pilot payment program to correct the existing problems, it had 3 objectives: (1) separate the oncologist's income from drug sales, (2) retain the medical oncologists' personal incomes at current levels, and (3) create an objective performance measurement system that becomes the basis for future payment increases."

—Lee N. Newcomer, MD, MHA
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THE AMERICAN JOURNAL OF MANAGED CARE

Payer Management of Oncology Gets Serious

Health Plans Continue to Seek Methods to Curtail Cancer Costs

Michael Snyder, Lee Goldberg, and Tracey Ryan

Oncologists perceive the current degree of payer oncology management to be significantly more aggressive than payers report.

Analyzing payer management of oncology over the past few years, a major trend has emerged—payers intend to increase their management of the category. Health plans continue to seek methods to curtail the costs associated with cancer care without diminishing the quality of that care. Indeed, both payers and oncologists anticipate significant increases in the aggressiveness of payer oncology management over the next 2 years.

According to the data collected in the most recent edition of *The Zitter Group's Managed Care Oncology Index*, just 38% of payers currently feel confident in their organizations' ability to effectively manage oncology. Although this number represents a significant increase from the 25% who reported such confidence 6 months ago, it is clear that payers have a long way to go to exert extensive control over cancer care.

In anticipation of the expected management increases, oncologists and practice managers indicate a growing resignation to payer influence on oncology practice. However, oncologists also perceive a slight decrease in the level of payer management aggressiveness from 6 months ago. This decline in reported restrictiveness may be due to adaptation by oncologists and practice managers to the policies already in place, as payers do not cite any corroborating changes in policy.

All stakeholders expect the degree of management intensity to ramp up over the next 2 years. Oncologists, however, expect a more dramatic increase than do payers. Sixty-five percent of oncologists expect a high degree of management aggressiveness by 2013, whereas only 21% of payers say they will have highly aggressive management policies in place by then. Oncologists also perceive the current degree of payer oncology management to be significantly more aggressive than payers report. Currently, only 7% of payers report having highly aggressive oncology management policies, whereas 30% of oncologists feel the level of payer management is highly aggressive (Figure 1).

Waste and Excess Cost

As the cost of oncology care continues to rise, increases in management efforts by payers appear to be inevitable. In fact, payers believe that nearly 23% of current costs could be eliminated from the delivery of cancer care without negatively impacting health outcomes. Oncologists and practice managers share similar sentiments, but not to the degree expressed by payers. Oncologists feel 18% of costs can be shaved, whereas practice managers see that number slightly lower, at just below 16% of costs.

In their efforts to decrease costs, payers will continue to increase their use of PA requirements, preferred distribution channels, treatment guidelines, clinical pathways, and companion diagnostics.

Payers perceive the greatest degree of wasteful spending coming from excessive end-of-life treatment and inappropriate drug utilization. Eighty-three percent of payers believe inappropriate drug utilization helps to drive excess cost. The majority of payers define inappropriate utilization as utilization outside a compendia-listed use. Conversely, while oncologists believe adherence to compendia improves care, they insist off-label prescribing is critical to providing the best quality care.

Furthermore, 43% of payers see suboptimal distribution of prescription drugs—such as buy and bill versus specialty pharmacy—as a significant driver of excess costs. That said, only 33% of payers currently require drug distribution through a third-party vendor. The number of plans utilizing specialty pharmacy providers (SPPs) and/or pharmacy benefit managers could see a sizable increase as payers attempt to rein in costs without harming care quality.

Figure 1. Aggression of Oncology Management

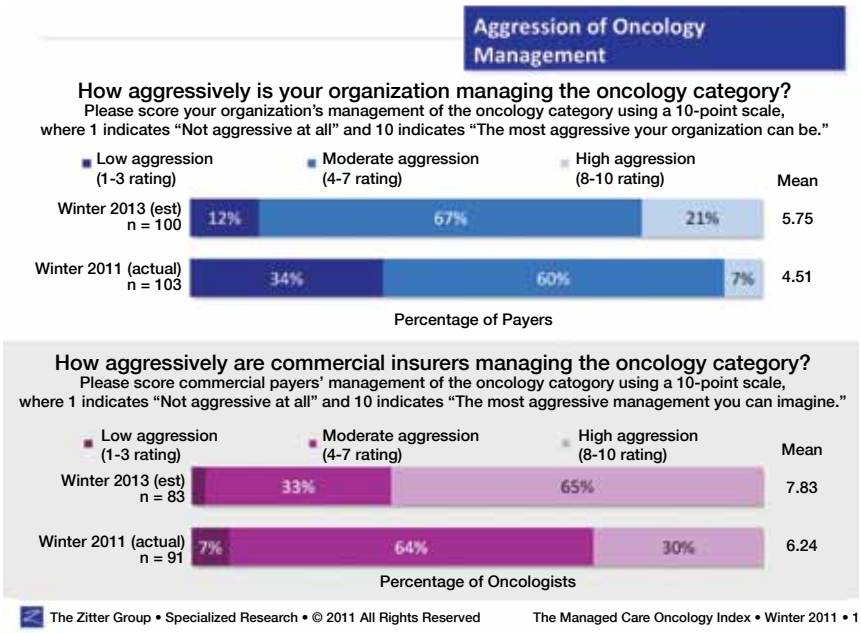


Figure 2. Payers' Preferred Distribution Channels for Infused Oncology Therapies

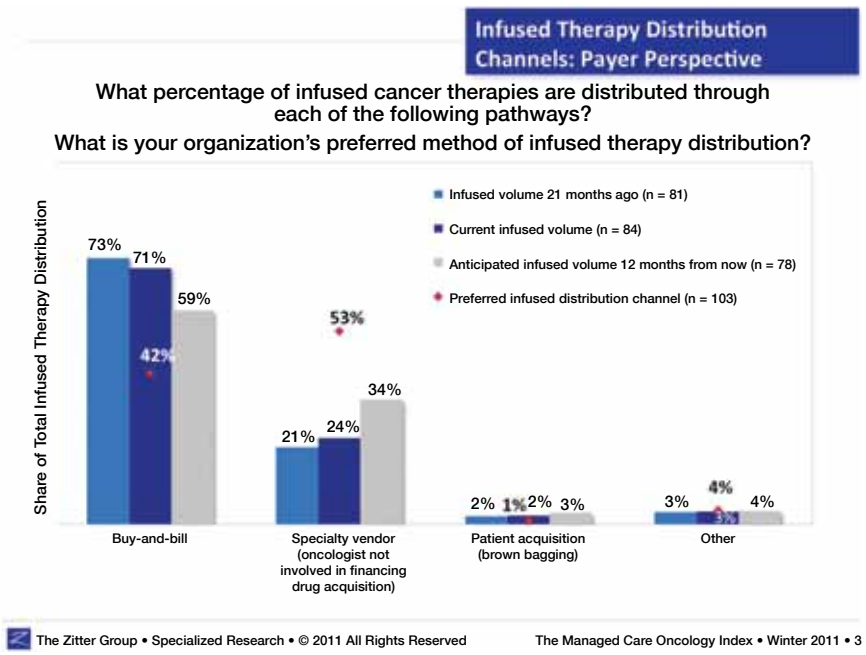
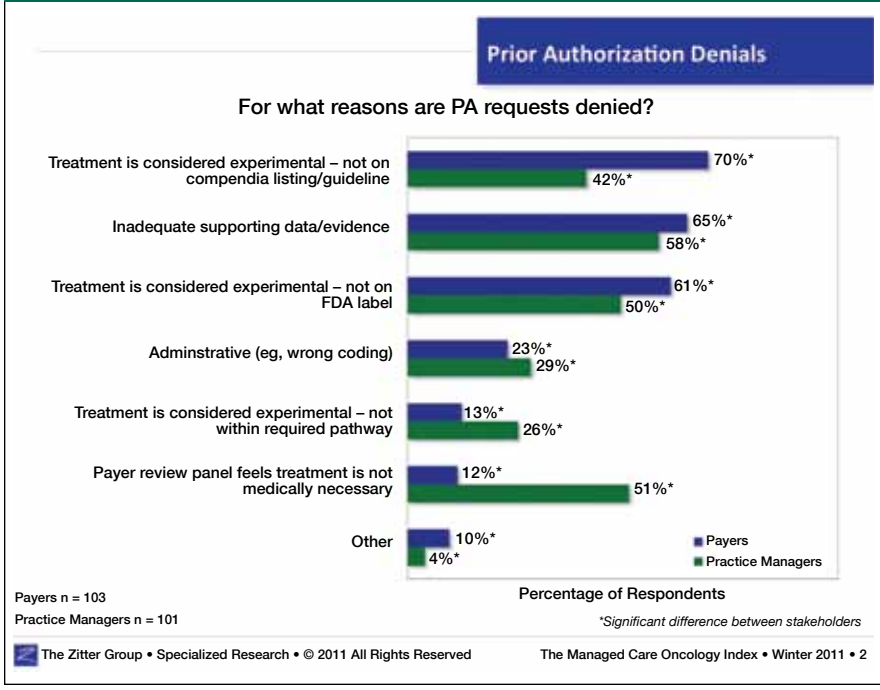


Figure 3. Reasons for Prior-Authorization Denials



Distribution Changes Coming

During the next year, payers anticipate shifting infused oncology therapy distribution away from buy and bill in favor of their preferred distribution channel, specialty vendors (Figure 2). Currently, more than 70% of infused therapies for oncology are distributed via buy and bill, with average sales price as the primary method of reimbursement used by payers. Providers have felt the pain: 36% of oncologists and 54% of practice managers report declines in practice revenue since moving to average sales price reimbursement. Payers now are looking to SPPs as the next step in minimizing excess reimbursement costs in oncology care.

Already, 30% of practice managers have experienced payer attempts to limit their ability to buy and bill for oncology therapies through contract terms. The majority of these contract terms specified either voluntary or mandatory vendor requirements, eg, specialty pharmacy. This trend has been well established with oral oncology therapy distribution, and payers anticipate a further shift away from off-site retail in favor of the specialty vendor channel for oral distribution over the next year.

The reality remains that payers are indeed taking a more direct role in oncology management.

Management Through Prior Authorization

Prior authorizations (PAs) remain the most prevalent and impactful management method utilized by payers in oncology management. Although widely used and shown to impact both oncologist and practice manager prescribing behavior, PAs are not fully achieving payer goals. The primary payer objective for oncology PAs is to limit inappropriate utilization, one of the perceived key drivers of excess costs in cancer care. However, just 19% of payers report having met this objective successfully.

There is significant disparity between payer, oncologist, and practice manager perception as to the impact of oncology PAs. While payers believe their PAs take a provider's office an average of just 16 minutes to complete, oncologists and practice managers report them taking significantly more time, with average durations of 38 minutes and 50 minutes, respectively. Furthermore, payers report denying 38% of all PA appeals, whereas practice managers report that nearly 9 out of 10 appealed requests are eventually approved. Payers and practice managers also differ greatly when it comes to the perceived reasons for a PA denial. Payers report denying PA requests primarily for treatments not on compendia listings/guidelines or the FDA label, whereas over half of practice managers report denials arising due to payer perceptions of a lack of medical necessity. Just 12% of payers report the last to be true (Figure 3).

Although there remains a degree of disconnect between payer management policies and their perceived effect on oncology practices, the reality remains that payers are indeed taking a more direct role in oncology management. In their efforts to decrease costs, payers will continue to increase their use of PA requirements, preferred distribution channels, treatment guidelines, clinical pathways, and companion diagnostics. Oncologists and practice managers seem increasingly, if begrudgingly, to accept these management tools as the inevitable evolution of cancer care management. **EBO**

Michael Snyder, sales and marketing analyst, The Zitter Group.

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Tracey Ryan, senior analyst, The Zitter Group.

All figures and numbers in the article are based on the findings of the Winter 2011 edition of The Zitter Group's Managed Care Oncology Index (MCOI). The MCOI is a semi-annual, multi-client study surveying approximately 100 payers, 100 oncologists, and 100 oncology practice managers. Started in 2006, the survey explores a wide range of payer oncology management issues, including physician reimbursement, prior authorization, patient cost-sharing, specialty pharmacy, site of care dynamics, practice economics, and clinical guidelines.

THE AMERICAN JOURNAL OF MANAGED CARE

Complexity of Drug Shortages
(continued from cover)

accelerate regulatory processes that help resolve drug shortages.

Dr Link recently spoke with *Evidence-Based Oncology*. The ASCO president also serves as the Lydia J. Lee Professor of Pediatric Hematology/Oncology at Stanford University School of Medicine and Director of the Bass Center for Cancer and Blood Diseases at the Lucile Salter Packard Children's Hospital at Stanford.

Q: How common are drug shortages?

MPL: Let me start by saying that this is an issue that is not only related to oncologic drugs. It relates mostly to generics, but includes antibiotics and aesthetic drugs as well as oncologic drugs and many others. I think it is now getting more attention because there has been a crescendo effect, almost a tripling of the number of drugs being followed that are in short supply over the last 5 years. There are hundreds of drugs in short supply, versus 20 or 30 in years past.

The reason? That's a bit more difficult. The companies don't have to announce the reason for a shortage, so we really don't know the reason in more than half the cases. Sometimes it's a manufacturing problem, meaning they're having difficulty producing a sterile injectible, because that's what most of the drugs in short supply are. There can be issues the drug precipitates, or a problem with the line. I understand one manufacturing plant was closed down by the FDA because they had a number of problems, and that creates a shortage because there are very few manufacturers making a given drug. If there's 2 and 1 goes out of business for a while, that creates a shortage.

Q: It sounds like the bigger issue is having some sort of advance notice that you know this is going to happen, so you can make alternative treatment plans.

MPL: Well, now you're on to the solution, but I want to make sure that another problem is highlighted. That is that there is not much profit to be made on these drugs, certainly the oncologics. If a company is having problems making the drug that would require retooling and expense to solve, and they're not making much money on the drug, there's not much incentive to fix the problem. Also, because of the limited profits, these companies may have a different drug they can make, with a better business plan, and so there's nothing to stop them from just ceasing to make the drug, as a business decision. Given that, the solutions are variable depending on what the real problems are, but economics has to be considered a key factor. Regarding advance notification, companies are not required to notify the FDA they're going to stop making a drug if it is not listed as a medically necessary drug. Admittedly, if the FDA has advance notice, they can do something preemptively to prevent a shortage. They can explore alternatives like importing a drug from a source outside the United States where the manufacturing is FDA approved, try to induce somebody else to make the drug, et cetera. The longer the lead time, the more clout the FDA might have. The penalties for not notifying the FDA, even if it's a medically necessary drug, are not terrible, so there's not much incentive for the companies to let people know. One issue that has been raised is that advance notification actually could exacerbate the problem, because if it's known a shortage is going to happen, distributors might buy up supplies, and there would be hoarding of drugs both by the hospitals and larger users, as well as distributors.

"For these drugs there is no work-around, and not just for pediatricians, but for medical oncologists as well—if you don't have cytarabine and daunomycin, you just can't treat the most common form of adult leukemia."

—Michael P. Link, MD

Q: Can you tell me a little more about the Preserving Access to Life Saving Medications Act? Is that going to help solve this problem so it becomes less of an economic situation for the manufacturers?

MPL: I don't know if that's going to solve the problem. One of the key things about this proposal is, number one, to focus attention on the issue. It would certainly do that. Early notification is not going to solve the problem. But, I think this is a good first step. It's important because at least it's focusing attention on the issue where we can hope to get to the bottom of the true nature of the drug shortage, and be more intelligent in how we address it.

Q: What kind of impact have you seen when all of a sudden a medication that you need to prescribe to a cancer patient isn't available? What are the implications there?

MPL: I have faced this situation a couple of times, and it's devastating. I first became aware of this problem when a drug we used in the treatment of lymphoma became unavailable. I prescribed it, ordered it, and our pharmacy said, "We don't have any." That's when I realized it wasn't just that drug in short supply, but a number of others, which is how ASCO got into this. In that case, there was already an effective and well-known work-around, an alternative medication that was also available and cheap; it was not on patent, and we could be pretty sure the outcome for the patient would not be affected. The second area where we thought we would run into trouble was in the shortage of cytarabine and daunomycin, which are both necessary to treat leukemia. For these drugs there is no work-around, and not just for pediatricians, but for medical oncologists as well—if you don't have cytarabine and daunomycin, you just can't treat the most common form of adult leukemia. And we need them for treatment of childhood leukemia as well. So, this is where there would be a real impact on patient care. The FDA did step in and provide a supply of cytarabine. Our pharmacist got a supply, with the unfortunate consequence that it was obtained at a substantial markup. So, that's one possible solution. Sometimes the drug is in short supply and there is no work-around, and then one has to consider the unpleasant option of changing a patient's therapy. That could involve telling a patient we don't have the drug now, but we could have the drug available, let's say, next week. That creates additional anxiety.

I think all oncologists know that delaying therapies and increasing the time between therapies is not a good thing. For some patients, even if they have delays they'll be cured, and for some it may not make a difference, but in the aggregate, we know that having delays in therapy is going to be harmful, that the cure rates of curable cancers will be lowered. An alternative would be to use a substitute. With cisplatin, which is the mainstay drug in the curative therapy for testicular cancer, there's another platinum analogue available, carboplatin, but it's less effective. So, we can give a regimen which we know is suboptimal, if you will, but we don't know the effect it will have on an individual patient. We know that the cure rate for, let's say, 1000 patients will be less than for cisplatin, but it's not as if we can't cure any patient without cisplatin. So, we could do that—with a great deal of anxiety and trepidation.

Q: If you had to use a secondary drug, would you have to use more of it for a greater length of time to have the same impact as your drug of choice?

MPL: I don't know that we have that information in that kind of detail, but we'd have to use a higher dose. We try to use regimens where we have some track record so we know what to do. In pediatric oncology, for example, we've done many studies where we take a standard regimen and add a new drug, and we prove that it adds to the cure rate. It may add 5, 10, 15 percent. We know we can cure some children without that drug if it's now in short supply; we just know we would be curing fewer of them. But, I don't know if we know that we could make up the difference by giving the other drugs more intensively, or at a higher dose, or longer. I don't think we've ever done those kinds of studies. We try to prove that a drug adds to the recipe, and then we assume we will have that drug available. One of the horrible things is, we've spent a lot of time proving that these drugs work, and now that they're unavailable, saying to a family, we do know what should be given, but we can't because the drug is unavailable, is a conversation that is very uncomfortable.

Q: Is there a cost impact?

MPL: Society will bear the cost, but it's not clear how it will break down. Let's start with the example I gave you where our institution was able to get a drug that is necessary, but paid more for it. It's not clear the patients will get reimbursed for the difference, and it's not clear that we will bill the difference. The hospital will have to eat that cost because that's the cost of obtaining the drug which we bear. There are times when a patient will be offered a drug which is a more expensive version. And, of course, that will add cost to the healthcare system. But, that's what you have to do when a drug is in short supply. Costs that are being added are, first, using a more expensive drug that maybe we think is effective, but which is not on the drug label in terms of its indication for use. The insurance companies may not reimburse the patient for use of the drug. The other costs are, of course, pharmacies and practices spending money, time, and resources rounding up supplies of the drug. And then we know that when you start using drugs that you're not used to using, you're going to have to take more time to figure out dosing. It's not second nature. You have to think about it more, and it also increases the opportunity for errors. If you made a medication error it would certainly add costs and potentially serious problems, and there has been documentation that such things have occurred. Those are additional costs to the system if not to an individual patient.

"Let's start with the example I gave you where our institution was able to get a drug that was necessary, but paid more for it. It's not clear the patients will get reimbursed for the difference, and it's not clear that we will bill the difference. The hospital will have to eat that cost because that's the cost of obtaining the drug which we bear."

—Michael P. Link, MD

Q: In talking about other areas that are affected as far as therapeutic areas, are there certain ones prevalent besides oncology, or is it just really across the board?

MPL: I think most areas are affected. Anesthetic drugs and antibiotics are among the leading agents, but cardiovascular drugs are affected as well. The reason the cancer drug issue is so compelling is that there are so few work-arounds. We don't have that many oncologic drugs, and for most of the indications, there are not good, verified substitutes. Whereas one can argue that for most antibiotics there's an alternative, if you forget about the cost and other details. In anesthesia the argument I would make is, you can still put people to sleep without Propofol, which is one of the drugs in short supply. It's very convenient, it's got a good toxicity profile, but there are other drugs we can use, maybe not as conveniently.

In cancer, though, especially in pediatric oncology, without these drugs we really can't operate. About 80 percent of children with cancer can now be cured almost entirely with these generic drugs that are off patent, and yet many of them are in short supply. It is a crisis because without those drugs we're back to where we were in the 1960s and 1970s. One disease for example, osteosarcoma, is a tumor where we now cure probably about 70 percent. And yet of the 3 drugs used for the treatment of osteosarcoma, doxorubicin is in short supply, cisplatin is in short supply, methotrexate with leucovorin is in short supply, and the leucovorin rescue which is necessary to give the methotrexate is in short supply. So, if you're a physician who takes care of osteosarcoma, or a patient, that's a pretty formidable obstacle.

From our point of view it's unconscionable when we have a curative therapy that we know about, but we're unable to deliver it because of the unavailability of a drug which has been around for 20 to 30 years. This is what we're up against and what is so frustrating for us as oncologists and for our patients.

Q: As ASCO president, do you have more influence?

MPL: Yes, I have influence with ASCO. Since we've identified this problem, ASCO has been extremely active in advocating for our patients, the people we serve. We were involved in the drug shortage summit in November. In fact, that bill [Preserving Access to Life-Savings Medications Act] really came directly out of the summit. If you look at the legislation and recommendations from this summit, it was almost a cut and paste. So we're happy to see we had some influence, though we're not convinced it will solve all the problems related to the shortage. Our government relations staff has been very active on the Hill looking for individual legislators who will take an interest in this. When we were up on the Hill in May to brief individual congressmen and senators, I was disconcerted to find how few of them really were aware of this shortage. By the time we had this Hill briefing in July it was standing room only. So very clearly this has gained some momentum.

I think it's important not to create a panic among patients who are already very anxious about their prospects, you know, cancer patients undergoing treatment, because many of them may not be affected by this at all. Their therapies have nothing to do with the drugs that are in short supply, or where they are getting treated the drug supply is not an issue. And for some patients, as in my own example that I gave, there is a very effective and well-known work-around, so their therapy will not particularly be affected. I think we do want to encourage people on an individual basis to talk to their physicians about the shortage and what the impact will be on their care.

Q: That's a huge thing for our audience—cost-effectiveness and still being able to increase quality of care.

MPL: Managed care managers should be aware that there are costs to the system which will have an impact on them. Using a substitute may cost more. The procurement charges may be higher because of supply and demand and because hospitals, and practices particularly, are forced to spend more of their resources trying to find sources of drugs. Those all impact the cost of care. Obviously, our major concern is the effect this is having on cancer care in our country. It's not just confined to the United States, it's a problem elsewhere also, so we're hoping we can come to some sort of creative solution. It will be a combination of entrepreneurial things, legislative things, it's going to be more than 1 solution to this problem, but we hope it can be solved before it becomes a larger crisis. **EBO**

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THE AMERICAN JOURNAL OF MANAGED CARE

Are We Winning the War on Cancer?

The Challenges Facing Oncologists Are Formidable

Ted Okon, MBA, and Lee Schwartzberg, MD, FACP

This year, we mark the 40-year anniversary of the National Cancer Act. The law expanded the scope and funding of the National Cancer Institute, among other initiatives, in what has become known as the "war on cancer." Looking back over the years, it is indisputable that we have made dramatic inroads in fighting cancer. A just-released report by the Centers for Disease Control and Prevention estimates that the number of survivors of cancer in the United States has increased from 3 million in 1971 to 11.7 million in 2007.[1] Yet cancer still claims the lives of more than half a million Americans each year and ranks close behind cardiovascular disease as the leading cause of death.[2] In this article, we offer our perspectives on how the war on cancer is going from the clinical and policy front lines and speculate on what the future holds.

Battles Have Been Won, With Some Impressive Results

There is little debate that cancer care delivery in the United States has evolved dramatically in the past 40 years and has produced impressive results. Aided by therapeutic and delivery advances, fellowship-trained oncologists have set up private practices across the country that have moved cancer care from the inpatient, academic center complex to the outpatient, community setting. Today, 4 of 5 Americans battling cancer are treated close to home in independent practices or those affiliated with hospitals.[3] The community model of cancer care has provided high-quality, affordable, and accessible treatment to patients with cancer.

Oncologists have been aided by significant advances in how they diagnose, treat, and manage cancer. For instance, the death rate from breast cancer decreased by approximately 2% per year between 1990 and 2006.[4] The multifactorial reasons for this decrease include widespread use of screening tests—such as mammography, which has increased early detection—as well as improvement in treatment in the adjuvant and metastatic setting. We can now realistically talk about certain metastatic cancers as chronic diseases, given that patients often live many years with good quality of life.

These encouraging results extend to the entire population. The increase in cancer mortality rates has been reversed, and 5-year survival rates for the United States demonstrate the strength of our cancer care delivery model. For example, American women have a 63% chance of living for at least 5 years after a cancer diagnosis compared with 56% for European women; American men have a 5-year survival rate of 66% compared with a rate of only 47% for European men.[5]

Public Policy May Stand in the Way of Victory

Unfortunately, public policy has changed the reimbursement model for Medicare, which accounts for approximately half of the payments for cancer care and threatens the advancements made to date. The intent of the Medicare Modernization Act of 2003 was to better balance the payment for cancer drugs and medical services. However, the law left shortfalls in the reimbursement of services, which have been exacerbated by additional payment cuts made by the Centers for Medicare & Medicaid Services. A study that was based on actual practice costs and completed by the policy firm Avalere Health estimated that Medicare reimbursed only 57% of the cost of delivering cancer care in 2009.[6]

Because Medicare is such a large payer, it exerts inordinate influence over the reimbursement system, with an escalating number of private payers following Medicare rates. It is increasingly difficult for private practices to operate under conditions in which Medicare reimbursement prevails. As a result, noncompensated but critical services—such as nutrition and counseling—are being abandoned as a result of lack of funding. Compounding the shortfalls in the reimbursement of cancer care is Congress' inability to fix the overall Medicare payment system on the basis of the sustainable growth rate (SGR). After a series of short-term patches during 2010, Congress managed to pass a bill averting a severe cut in Medicare payments until January 1, 2012. If Congress does not act to patch or fix the flawed SGR-based payment system, a 29.5% cut in Medicare rates will become effective.

Further clouding the environment for oncology is the Patient Protection and Affordable Care Act (ACA), the healthcare reform bill that passed into law in 2010. The law includes some positives for cancer care, such as the elimination of annual and lifetime insurance caps, coverage for preventive services like colonoscopy and mammography, and prohibition of exclusion of the routine costs of cancer care for patients in clinical trials by private insurers. However, several provisions in the law are disconcerting to oncology practices. Chief among these is the creation of the Independent Payment Advisory Board, which is charged with simply cutting Medicare spending to providers when certain targets are exceeded—a type of SGR on steroids.

Because of reimbursement cuts from both federal and private payers and the general economic climate, oncology practices are being forced to operate in an environment of tremendous uncertainty. Any type of business planning beyond the current year is meaningless and makes running the business side of an oncology practice difficult at best. A practice impact tracking report shows that 199 cancer treatment sites have closed during the past 3 years, and an additional 369 oncology practices are under financial pressure.[7] With the unpredictability of revenue streams and adverse market conditions, momentum is building for alternative affiliations. Many oncology practices are entering into arrangements with hospitals that include outright purchase, professional service agreements, and comanagement opportunities. It is possible that such arrangements may influence patient access to care in the future.

"Because of reimbursement cuts from both federal and private payers and the general economic climate, oncology practices are being forced to operate in an environment of tremendous uncertainty."

—Ted Okon, MBA, and Lee Schwartzberg, MD, FACP

The greatest uncertainty facing oncologists and all physicians is the extent to which the ACA will be implemented. Republicans in Congress have launched a legislative assault to defund and repeal provisions in the law, and the Supreme Court is likely to decide whether the cornerstone of reform—the mandate that will require all Americans to have insurance or pay a penalty—is constitutional. Regardless of the final fate of the ACA, it is clear that this landmark legislation has already profoundly influenced the thinking of practices, hospitals, and payers, given the emphasis on coordinating care and promoting quality and cost-effective initiatives in medicine.

Oncologists' Drive to Innovate Gives Hope

Just as oncologists created and evolved the world's best cancer care delivery system, this culture shift has inspired many to further innovation despite the challenges placed in their way. Consultants in Medical Oncology and Hematology in Drexel Hill, Pennsylvania, which is led by John Sprandio, has reengineered its approach to become the first community oncology practice in the country to earn the highest, level III recognition from the National Committee for Quality Assurance under its Patient-Centered Medical Home Program.[8] At the time of diagnosis, physicians in this practice assume primary responsibility for the patient's cancer treatment as well as for the coordination of all the patients' other medical care, extending through the development and implementation of a survivorship plan. At the heart of this patient-centered medical home model are specific definitions of quality and value in the delivery of cancer care. The promise of healthcare reform—namely, enhancing quality and controlling costs—is becoming a reality.

Other community oncology practices are pursuing novel innovative reimbursement initiatives with payers in attempts to forge win-win relationships that preserve and foster the delivery of quality cancer care. Several practices from around the country are working with UnitedHealthcare on a program built around agreed-upon treatment guidelines and episodes of care for 19 different cancers and disease states on the basis of stage of cancer. In this scenario, the drugs become a pass-through item and are not the drivers of operating margin. Risk is shared by both the practice and the managed-care organization. By comparing actual with planned use within and across practices, this program has the potential to continually provide guidance to move toward best treatments for specific diseases and stages.

Other practices are looking to increase participation in networks that clinically integrate care by using prespecified care plans that are based on national practice guidelines. In oncology, there is a strong evidence base that focuses on clinical trial–tested regimens, which are constantly updated by such authorities as the National Comprehensive Cancer Network and the American Society of Clinical Oncology. These guidelines offer the opportunity for oncologists, who are among the most prevalent adopters of electronic health records in medicine, to continually monitor compliance with process in treating patients according to prespecified plans and to scrutinize patient outcome. Community oncologists are thus well poised to be leaders in accountable care organizations, as these are formed under hospital, payer, or physician leadership.

This fundamental change in the way cancer care is organized and delivered comes against a background of groundbreaking discovery into the basic biology of cancer. The understanding that a finite number of critical oncogenes and pathways drive cancer growth and metastasis has reached a level at which rational therapeutics can be designed against cancer tissue–specific targets, enhancing efficacy and reducing toxicity. Already, early fruits of this labor have been recognized with US Food and Drug Administration approval of multiple agents against previously difficult-to-treat cancers such as renal cell carcinoma. Recognition that every tumor type is itself composed of multiple subsets that are driven by different mutations with each possibly requiring a different approach will actually add to the complexity of ensuring appropriate care, as the decision tree and system support needs will be large. Improvements in health informatics that are user friendly and easy to implement in the clinic hold the promise to aid in care delivery and allow monitoring of quality cancer treatment in the emerging age of personalized cancer care.

Public Policy May Decide the Outcome of the War

There is no doubt that we have made positive inroads in terms of winning the war on cancer. The tools are in place and increasing in both sophistication and precision for additional progress toward making cancer a true chronic disease if not ultimately to find cures. We question, however, whether public policy will erect insurmountable barriers that ultimately make winning the war difficult if not impossible. With an increasing demand for cancer care that is driven by the demographics of an aging population that is far outpacing the supply of oncologists and the ongoing transformation of the reimbursement system, the challenges facing oncology are formidable. The first stage of the war involved scientific advancements, ingenuity, and entrepreneurial spirit in developing the cancer care delivery system that is the model for the world. The next stage will require the collaboration of oncology providers and payers to explore innovative ways of preserving and developing the model even further to foster quality and cost-effective cancer care. **EBO**

Ted Okon, MBA, is executive director, Community Oncology Alliance. **Lee Schwartzberg**, MD, FACP, is medical director, West Clinic.

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Putting Value Into Practice *(continued from cover)*

Center for Value-Based Insurance Design (www.vbidcenter.org), discusses V-BID and its value in oncology, along with Jonas de Souza, MD, instructor of medicine, Section of Hematology/Oncology at the University of Chicago Medical Center.

What is V-BID?

AMF: The basic V-BID premise is to align patients' out-of-pocket costs, such as co-payments and premiums, with the value of health services. This approach to designing benefit plans recognizes that different health services have different levels of value. By reducing barriers to high-value treatments (through lower costs to patients) and discouraging low-value treatments (through higher costs to patients), these plans can achieve improved health outcomes at any level of health care expenditure.
JDS: In oncology, V-BID would further consist of a reimbursement model that promotes evidence-based medicine. At the same level of health care expenditure, it would promote a higher utilization of interventions with higher efficacy and/or with a higher level of evidence, as shown in clinical trials, at a cost of a lower utilization of interventions with marginal benefits and those that are not supported by evidence.

How would you define value in oncology?

JDS: In general terms, value is the right therapy to the right patient at the right time, at the right cost. In other words, value has several domains, which include: a) the safety of the intervention, where toxicities should be kept to a minimum; b) efficacy and effectiveness, where interventions with incremental proven benefits, as shown in clinical trials, should be considered of value; c) out-of-pocket cost to the patient and costs to society, where an intervention that is safe and has efficacy should not place a cancer patient under a financial strain. There have been several discussions among stakeholders about the definition of value, but as ground rules, the wrong value is when the intervention provides no incremental survival or quality of life benefit; when the intervention has an unacceptable toxicity profile; or when a life-saving or prolonging intervention is out of reach to a particular patient for financial reasons.
AMF: In addition, there is lots of evidence that suggests that patients do not always use high-value, potentially life-saving oncology services, even when they face no financial barrier. However, it is also well established that when patient barriers are reduced—such as in a V-BID plan—utilization of these services will increase significantly.

What would be examples of how V-BID can be applied in practice?

AMF: If any intervention were to be demonstrated to enhance clinical outcomes (our primary goal) or constrain healthcare expenditures, it would be included in a value-based approach. V-BID programs outside of cancer have rapidly expanded beyond drugs, to include screenings, diagnostic tests, and specific clinician groups and delivery systems. Certain V-BID programs encourage patients to receive care at cancer centers of excellence, because of their superior quality, not because they cost less.
JDS: In practice, a system where a screening colonoscopy in a 30-year-old man with a genetic syndrome predisposing to colorectal cancer, such as hereditary nonpolyposis colorectal cancer, should be done at virtually no cost to the patient. On the other hand, the same procedure, performed electively in another 30-year-old man with no predisposing risk factors, should have a higher copayment. Or, in the therapeutic realm, if intervention X provides a median survival benefit of 4 months in metastatic colorectal cancer, it should be valued more and have its copayment lowered and access improved to patients, when compared with the same intervention providing 2 months of incremental survival in metastatic non–small cell lung cancer.

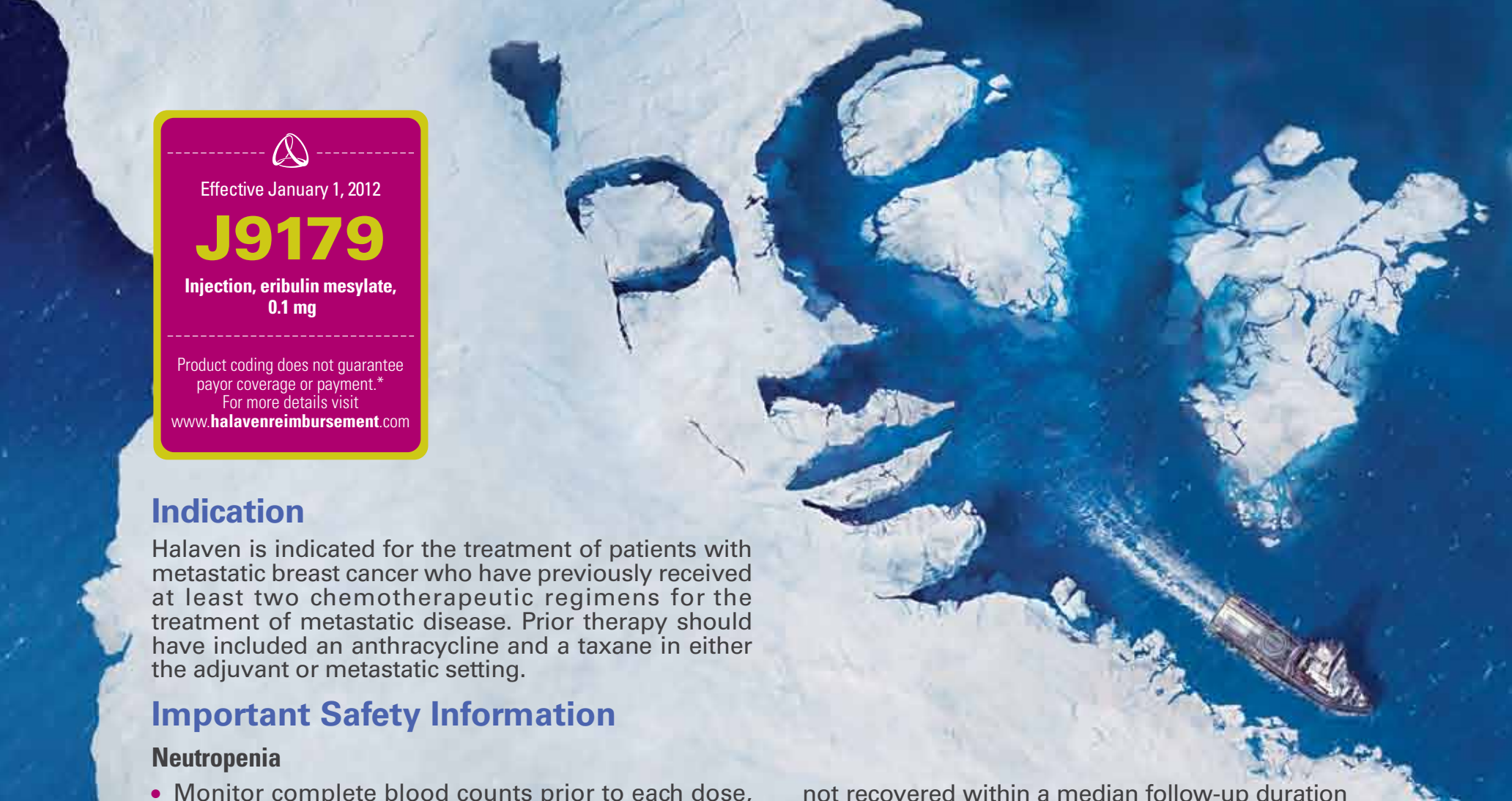
Jonas de Souza, MD

Under the V-BID model, what are some recommended high-value alternatives for managing end-stage cancer?

AMF: The sooner we move to a more "clinically nuanced," efficient and effective cancer delivery system, the better off all stakeholders will be. That is why we feel that patient out-of-pocket costs should not be exclusively based on the cost of a service, but instead be tied to the amount of clinical benefit for the money spent.
JDS: An easily overlooked and undervalued intervention in managing patients with advanced malignancies, when usually all therapeutic interventions have failed, is early introduction to palliative care services. They have been shown to improve survival and quality of life in this group of patients but still are undervalued when compared with more commonly prescribed, and usually off-evidence, therapeutic approaches. Patients should have access to these interventions facilitated.

Is there any movement from the stakeholders toward better aligning the value of oncologic interventions with patients' out-of-pocket costs?

AMF: The most important step forward is the regulations in the Affordable Care Act [Section 2713] supporting evidence-based cancer screenings being provided to all Americans without any cost sharing. Preventing cancer is their first focus; it is our hope that future endeavors will address treatment as well.
JDS: V-BID does not focus only on specific interventions. The recent trend in oncology toward clinical pathways is a similar model. In this system, payers promote interventions, usually therapies, which are shown to have improved outcomes at reduced costs, by giving financial incentives to providers and/or groups of practices to prescribe them. V-BID would also encourage the greater utilization of these services by facilitating access and/or providing incentives to patients to use these high-value interventions. **EBO**



Effective January 1, 2012

J9179

Injection, eribulin mesylate, 0.1 mg

Product coding does not guarantee payor coverage or payment.*
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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.

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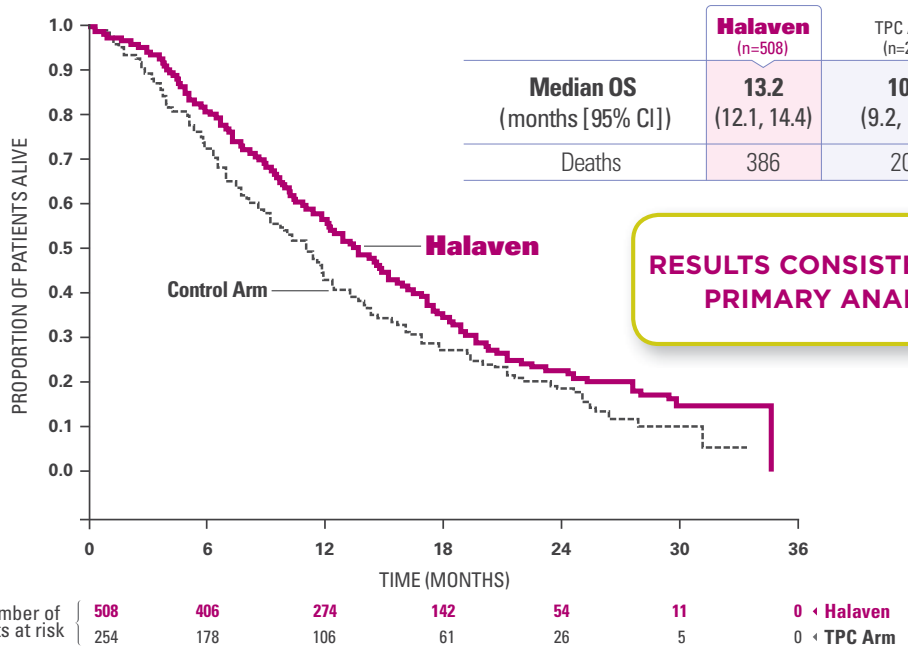
The Phase III EMBRACE* trial met its primary endpoint of overall survival (OS)[2,11]

- 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

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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]
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

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. 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

No formal PK trials were conducted with HALAVEN in patients with renal impairment. Available data suggests that no dose adjustment is necessary for patients with mild renal impairment (CrCl 50-80 mL/min). 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. 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

12.2 Pharmacodynamics

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

Targeted Products Yield Most Promising Results

A New Era in Targeted Treatment Has Begun

Melanoma is one of the most frequent cancers; more than 2 million Americans are treated for skin cancer annually. However, in its earlier stages, it can be easily cured by removal of the skin lesion.[1] "Melanoma is on the surface of the skin and therefore easily visible to patients, doctors, and other health professionals without the use of x-rays or invasive procedures," said Lynn Schuchter, MD, professor of medicine, University of Pennsylvania School of Medicine, Philadelphia. "Therefore, early detection is highly feasible. Most melanomas are cured with surgery because the melanoma is detected at an early stage of disease, before melanoma cells have the potential to metastasize." Schuchter explained, "Once melanoma metastasizes to distant sites, it is highly resistant to therapy." It caused an estimated 8700 deaths in 2010.[1]

Chemotherapy for advanced disease has yielded poor 5-year survivals for patients with metastatic disease—16% of those with metastatic melanoma survive 5 years post-diagnosis.[2] Dacarbazine is the only drug approved by the US Food and Drug Administration (FDA) for treating metastatic melanoma, and it is often ineffective.[3] In other words, the prognosis for patients whose melanoma has spread is generally poor, and very few therapies existed before 2011 that could make more than a marginal difference. Only recently have investigational products emerged that, alone or in combination, seem to yield positive responses in some patients.

Taking Advantage of the Body's Immune Response

Melanoma is one of the few cancers that trigger the body's immune response naturally.[4] The problem is that the response is easily overwhelmed by the malignancy. Ipilimumab, which was approved in March 2011 by the FDA, works by spurring the body's immune system to attack the tumor. The melanoma pipeline comprises several examples of investigational agents that seek to enhance the immune response, including therapeutic vaccines.

Vaccines

OncoVEX$^{GM\text{-}CSF}$. The therapeutic vaccine that is perhaps furthest along the pipeline is OncoVEX$^{GM\text{-}CSF}$, which is customized to the patient by using their own tumor antigens. This viral vaccine invades both healthy cells and melanoma cells, but it does not harm the healthy cells, only replicating within the malignant cells, according to the manufacturer, Biovex, which was acquired by Amgen in

PIPELINE PERSPECTIVE

Interview With Maria Lopes, MD, MS, Chief Medical Officer, AMC Health

Q. How are payers evaluating the value of newer, targeted melanoma therapies, such as ipilimumab and vemurafenib?

ML: As with other oncology agents, payers are evaluating new therapies primarily on the basis of the clinical trial data with efficacy and safety. We're using the label indication/appropriate use as defined by National Comprehensive Cancer Network to define coverage criteria. Since ipilimumab is an infused agent, it is covered through the medical benefit. Vemurafenib, an oral drug, may be managed through the pharmacy benefit. This may result in implications for patient cost share and pharmacy management.

Ipilimumab is administered intravenously over 90 minutes every 3 weeks, a total of 4 doses and $120,000. The marginal benefit in overall survival (OS) is 3.6 months, compared with GP vaccine and a marginal OS benefit of 2.1 months in the group receiving ipilimumab in combination with dacarbazine versus dacarbazine alone. Ipilimumab was approved with a companion diagnostic test for a biomarker to help in patient selection.

In contrast, vemurafenib is an oral agent given twice daily, with an FDA-approved diagnostic kit and a total estimated treatment cost of $37,000 to $56,400 for the average treatment duration of 4 to 6 months. Overall survival data are not yet available but trends in a favorable direction. To the extent that there is a biomarker associated with the drug to assist in identifying those who will have the highest likelihood to benefit from its use, the BRAF mutation is a requirement that will be incorporated into the prior authorization consideration for approval and will hopefully add to improved outcomes and provide clinically meaningful OS.

Q: Are they game changers for patients with metastatic melanoma?

ML: The goal of new treatments will be to enhance meaningful OS. With targeted therapy, the ability to identify who can benefit most from a treatment will hopefully lead to not only statically significant changes in OS but clinically meaningful OS (OS >6 months) versus best standard of care and go beyond progression-free survival and risk of recurrence to justify coverage and value. As we compare outcomes, it will become increasingly more important to payers, providers, and members to examine value as the margin of OS, safety in the context of the episode treatment cost, and how this compares with existing treatment options.

Q: From a payer's viewpoint, what are the most important clinical (or clinically based) outcomes that help you determine the value of an oncological medication? Are these outcomes generally being tested and reported by the manufacturers?

ML: As a payer, the end point with the most meaning to me is OS. The future of personalized medicine in oncology will require an evidence-based approach to define the best sequence of treatment options based on individual genomic patterns, and to deliver better efficacy, safety, or cost, which will define a rational treatment/pathway approach to available treatment options. That will require identifying through biomarkers/compendium diagnostics those who can benefit most from specific agents or combination therapies, by adding meaningful improvements in OS.

Q: Therapeutic vaccines are featured prominently in the melanoma pipeline. How can lessons learned from vaccines like sipuleucel-T (Provenge) be applied to understanding the value of these investigational immunostimulatory products?

ML: Provenge tested the concept of value. Although it came with a unique mechanism of action, using autologous immunotherapy, the price was simply too high for the OS survival benefit. From the clinical trials, the median OS for patients receiving Provenge was 25.8 months compared with 21.7 months in the control group, at an episode treatment cost of more than $94,000. Despite this, the Centers for Medicare & Medicaid Services approved the drug for coverage and NCCN's Prostate Panel added Provenge as a category 1 treatment recommendation for patients with castration-resistant prostate cancer. As a result, Provenge is covered by most payers despite the modest marginal value.

Q: In oncology research most investigational agents are being tested not as monotherapies but in combined use with approved treatments. When trying to address value on a health tech assessment committee, how do these additive regimens complicate the calculation of cost-effectiveness?

ML: When comparing treatment options, it is important to keep in mind how the combinations will not only add to cost and possibly side effects, but in the real world, how we can control waste and noncompliance, if the agents are not being taken as prescribed.

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Date Updated	Company	Product	Mechanism of Action	Indication(s)	Stage	Licensee/Partner(s)	PDUFA Date[a]
11/11/2011	**AB Science**	Masitinib	Tyrosine kinase inhibitor (TKI)/c-kit inhibitor	Melanoma stage III or IV	Phase III	N/A	N/A
11/11/2011	**Celgene**	ABI-007 (paclitaxel derivative)	Antimicrotubule agent	Metastatic melanoma in treatment-naïve patients	Phase III	N/A	N/A
1/11/2011	**Agenus (formerly Antigenics, Inc)**	Prophage (vitespen)	Vaccine	Melanoma stage IV	Phase IIIa	N/A	N/A
11/11/2011	**AVAX Technologies**	Mvax	Vaccine	In combination with low dose interleukin-2 in patients with stage IV melanoma	Phase III	N/A	N/A
11/11/2011	**Bayer AG**	Nexavar (sorafenib)	Raf kinase inhibitor/ vascular endothelial growth factor receptor inhibitor (VEGFR)	In combination with standard chemotherapies after receiving 1 prior therapy of dacarbazine or temozolomide in patients with stage III or IV melanoma	Phase III	Onyx Pharmaceutical	N/A
11/11/2011	**Amgen**	OncoVEX$^{GM\text{-}CSF}$	Vaccine	In combination with GM-CSF in patients with metastatic melanoma	Phase III	N/A	N/A
11/11/2011	**Bristol-Myers Squibb Co**	Yervoy (ipilimumab)	Monoclonal antibody	Unrestable or metastatic melanoma	FDA approval 3-25-11	N/A	—
11/11/2011	**Bristol-Myers Squibb Co**	Yervoy (ipilimumab)	Monoclonal antibody	Prevent recurrence after complete resection of high-risk stage III melanoma	Phase III	N/A	N/A
11/11/2011	**Bristol-Myers Squibb Co**	Yervoy (ipilimumab)	Monoclonal antibody	Ipilimumab plus temozolomide in metastatic melanoma	Phase III	N/A	N/A
11/11/2011	**Eli Lilly & Co**	Tasisulam	N/A	Metastatic melanoma	Phase III	N/A	N/A
11/11/2011	**GlaxoSmithKline**	GSK1120212	MEK inhibitor	Patients with stage III or IV malignant melanoma previously treated with or without a BRAF inhibitor	Phase III	N/A	N/A
11/11/2011	**GlaxoSmithKline**	GSK2118436	BRAF protein kinase inhibitor	Previously treated BRAF mutant metastatic melanoma	Phase III	N/A	N/A
11/11/2011	**GlaxoSmithKline**	GSK2132231A	MAGE-A3 vaccine	Adjuvant therapy in patients with resected melanoma	Phase III	N/A	N/A
11/11/2011	**Merck & Co, Inc**	Temodar (temozolomide)	Cytotoxic alkylating agent	Stage IV metastatic melanoma	Phase III	N/A	N/A
11/11/2011	**Merck & Co, Inc**	Temodar (temozolomide)	Cytotoxic alkylating agent	In combination with radiation therapy to the brain in treating patients with stage IV melanoma	Phase III	European Organization for Research and Treatment of Cancer, National Cancer Institute (NCI)	N/A
11/11/2011	**Novartis AG**	Tasigna (nilotinib)	TKI	Metastatic and/or inoperable melanoma harboring a c-kit mutation	Phase III	N/A	N/A
11/11/2011	**Pfizer**	Tremelimumab	Monocolonal antibody	Treatment-naïve patients with surgically incurable metastatic melanoma	Phase III	Debiopharm	N/A
11/11/2011	**Roche Holdings Ltd**	Zelboraf (vemurafenib)	BRAF protein kinase inhibitor	BRAF V600 mutation–positive metastatic melanoma	FDA approval 8-17-11	Plexxicon	—
11/11/2011	**Roche Holdings Ltd**	Zelboraf (vemurafenib)	BRAF protein kinase inhibitor	BRAF V600 mutation–positive advanced melanoma with brain metastases	Phase II	Plexxicon	N/A
5/27/2011	**Vical**	Allovectin-7	Tumor suppression gene therapy	In combination with dacarbazine in patients with stage III or IV melanoma	Phase III	N/A	N/A

FDA indicates US Food and Drug Administration; N/A, not available; PDUFA, Prescription Drug User Fee Act.
[a]No further clinical trial or regulatory submission activity since 2008.

March 2011.[5] The virus produces granulocyte-macrophage colony-stimulating factor (GM-CSF), which gathers dendritic cells, causing the rupture of the tumor cell. This releases GM-CSF and tumor-cell peptides into the local area. The dendritic cells collect the tumor-cell peptides, allowing the immune system to recognize and attack them.

In 2009, phase II testing of the vaccine in 50 patients with metastatic melanoma revealed overall survival at 2 years of 52%, and an objective response rate was 26% (stable disease rate of 20%).[6] Phase III testing is currently under way, and this OPTiM trial is expected to be completed in June 2012 (ClinicalTrials.gov, NCT00769704). The OPTiM trial compares the vaccine with the use of GM-CSF administered subcutaneously in patients with stage III (b-c) and stage IV (M1a-c) disease.

Prophage (vitaspen). Not all autologous vaccine-based therapies entering phase III trials have met with success. This vaccine (formerly known as Oncophage), which is developed using gp96 and other peptides from the patient's own tumor, was found to not improve survival in patients with stage IV melanoma compared with any other choice of therapy by the physician. In this phase III trial, only patients with better prognostic characteristics who were injected with vitaspen seemed to improve.[7]

MVax. In the case of MVax, from Avax Technologies, the phase II clinical trial results were encouraging, yet the phase III study was halted in 2010, not for safety reasons or poor outcomes, but because of a lack of capital. It is unclear as to when or if this phase III trial may be continued, or if an interim analysis of the study results will take place as planned.

Similarly, in 2005, CancerVax Corp halted its phase III trial of the vaccine Canavaxinin for late-stage melanoma not because of safety reasons but because it had not shown any benefit over placebo.[8]

Schuchter commented that overall, "Current approaches to vaccine development are still a major challenge. Unless there is a whole new approach to melanoma vaccines, I am not optimistic about the future of vaccines for patients with melanoma."

Allovectin-7. A plasmid that contains the genetic sequences for HLA-B7 and β2-microglobulin, Allovectin-7 is a receptor that activates T cells to provoke an im-

mune response.[9] This immunomodulator can be injected directly into the tumor lesion, which may help T-cell recognition of the malignancy and specific attacks on these specific tumor cells.[9] In phase II studies, Allovectin-7 injection in patients with recurrent or refractory advanced melanoma produced a 12% response rate, with a median duration of response of 13.8 months.[10] The phase III AIMM trial was begun in 2007 and compares Allovectin-7 with dacarbazine or temozolomide in patients who had not been previously treated with chemotherapy (ClinicalTrials.gov, NCT00395070). This trial is scheduled for completion in the third quarter of 2012.

GSK2132231A. GSK2132231A is a recombinant fusion protein with potential immunostimulatory and antineoplastic properties that is derived from the melanoma antigen MAGE-3 and protein D from *Hemophilus influenzae* (it is also referred to as a MAGE-3 + AS02B by the manufacturer). No clinical trial data using this agent have yet been made public, but a phase III trial called DERMA is currently enrolling patients to examine the use of GSK2132231A as adjuvant therapy for patients with resected melanoma (ClinicalTrials.gov, NCT00796445). Thirteen hundred patients will be enrolled, and the study is expected to be completed in December 2016.

Tremelimumab. This product, a fully human IgG2 monoclonal antibody targeted to CTLA-4, like ipilimumab, may summarize the key learning of research on melanoma to date: The shotgun approach to drug development in metastatic melanoma works poorly. In a previous phase III trial, tremelimumab failed to demonstrate a significant improvement in overall survival compared with temozolomide or dacarbazine in a cohort of patients without prior systemic treatment for their metastatic melanoma.[11] However, Pfizer came to an agreement with Switzerland's Debiopharm to revive plans for a clinical trial of tremelimumab in patients with a biomarker indicating it would most likely be effective. Under this arrangement, Debiopharm would be responsible for funding and running the phase III trial (not yet under way).[12] In October 2011, Pfizer granted global rights to the product to MedImmune, a subsidiary of AstraZeneca, for development of this product for other indications.[13]

Ipilimumab. Approved in March 2011 for use in non-resectable or metastatic (untreated) melanoma, its manufacturer, Bristol-Myers Squibb, is conducting additional trials to determine if ipilimumab is also effective in untreated metastatic disease when combined with dacarbazine (ClinicalTrials.gov, NCT00324155) and if it is effective as adjuvant therapy in patients with high-risk stage III disease (ClinicalTrials.gov, NCT00636168). Randomized phase II data have demonstrated 65% 1-year survival and 23% 3-year survival for the ipilimumab + dacarbazine combination in patients with chemotherapy-naïve advanced disease.[14]

Ipilimumab is a fully human monoclonal antibody targeted to CTLA-4, a molecule known to negatively regulate the immune system.[15] By inhibiting CTLA-4, ipilimumab can enhance the immune system's T-cell response to tumor cells. In its pivotal 3-arm trial, another BMS agent, gp100 peptide vaccine, which was dubbed MDX-1379, was used as the active control, despite the fact that no standard of care exists for this patient population. Patients were randomized to receive ipilimumab and gp100, gp100 and placebo, or ipilimumab and placebo. Compared with the median overall survival (OS) of the gp100 arm (6.4 months), both ipilimumab-containing arms produced significant improvements, with a median OS of 10.0 months in the combination therapy arm (P <.001) and 10.1 months in the monotherapy arm (P =.003). In addition to these promising data, ipilimumab is also in phase III testing as an addition to dacarbazine chemotherapy for patients with untreated advanced melanoma (ClinicalTrials.gov, NCT00324155). Clinical trials have identified potential toxic liver effects.

There is no evidence that BMS is proceeding with the developmental program for MDX-1379.

Focusing on Melanoma Cell Targets

Much research in metastatic melanoma has involved testing of agents on specific melanoma cell targets or biomarkers. The targeted medication that has received the most attention, vemurafenib, was approved along with its companion diagnostic test in August 2011 to treat patients with metastatic (late-stage) or unresected (inoperable) melanoma in patients whose tumors express the BRAF gene's V600E mutation, a driver of tumor growth. Other targets include c-kit, MEK, and Bcl-2 inhibitors. However, successful targeting is difficult, as demonstrated by Genta, which in May 2011 terminated its Phase III trial and development program for the Bcl-2 inhibitor oblimersen (Gentasense) for the treatment of melanoma.[16] On the other hand, GlaxoSmithKline's GSK2118436, a BRAF inhibitor, has entered Phase III testing (the first Phase III study is scheduled to be completed in June 2012), which if successful in clinical trials won't reach the market for some time (2014 at the earliest).

GSK1120212. Another targeted agent, GSK1120212, is an inhibitor of the MEK1 and MEK2 (MEK1/2) enzymes, preventing Raf-dependent MEK phosphorylation, resulting in antitumor effects in early-stage trials.[17] This GlaxoSmithKline product is the subject of multiple clinical trials for different oncology indications. For melanoma, it is being tested in an open-label, randomized Phase III study comparing

Placing a Heavy Burden

Melanoma Devastating to Patients...and Society

In 2011, over 70,000 Americans are expected to be diagnosed with melanoma and nearly 8800 will die of this disease.[1] Melanoma represents a modest fraction—approximately 4%—of all newly diagnosed cancers in the United States, but the economic burden of this disease is substantial. One recent study examined the annual direct costs of caring for melanoma patients in the United States who were at least 65 years of age, reporting the annual cost to be $249 million.[2] However, this drastically underestimates the actual economic burden of this disease because (1) only direct costs were measured (indirect costs were ignored), and (2) the patient population was restricted to those 65 years or older, which accounts for only 41% of the total melanoma patient population.[3]

A study published in 2009 used a comprehensive model of melanoma-related expenses to illustrate how costs differ at the distinct stages of disease, owing to the need for specific medical interventions and other healthcare expenditures.[4] Using this model to quantify the average melanoma healthcare costs per person for the 5 years after melanoma diagnosis at each particular stage, the authors reported that these healthcare costs increase dramatically with the stage of disease. They demonstrated that, for the earliest stage disease (in situ melanoma), 5-year expenditures were only $4648. This increased substantially with each later stage of disease. For example, patients with stage IA disease incurred costs of $11,115, and those with stage IIA disease had 5-year costs totaling $29,620. For patients with stage III or IV disease, however, average healthcare costs in the 5 years post-diagnosis increased sharply—to over $150,000. Not surprisingly, the relative distribution of costs among healthcare expenditures varied significantly by stage. Patients with in situ melanoma spent the bulk of their expenditures on treatment of the primary lesion (52%) and surveillance costs (27%). In contrast, patients with metastatic melanoma spent only 2% of their total expenditures on the treatment of the primary lesion and nothing on surveillance, but they used 73% on workup and treatment for metastatic disease and 9% on terminal care costs. When costs were grouped by intervention, the treatment of a metastatic tumor was by far the most expensive outlay, costing $116,294. However, adjuvant therapy with interferon-alpha for high-risk melanoma was also quite expensive, with a cost of $75,955. Among the most expensive single-item expenditures were radiation therapy ($15,999), surgical removal of a skin tumor ($7150), and hospitalization for neutropenic fever ($1535-$1800 per day).

Another way to measure economic burden of a disease is to examine productivity lost as a result of a disease. The Centers for Disease Control and Prevention (CDC) has published a study quantifying the productivity loss associated with melanoma. The authors reported that, on average, a person with melanoma loses 20.4 years of potential life as a result of the melanoma, which is almost 4 years more than that lost for malignant cancers as a whole.[5] Furthermore, the average melanoma patient will experience a lifetime earnings loss of $413,370 caused by his or her cancer diagnosis. This translates into an estimated annual US productivity loss due to melanoma of $3.5 billion (in 2006 US dollars). Productivity losses were not spread evenly among all ethnicities, however. Total productivity losses per person were lowest among non-Hispanic whites ($409,814) and highest among Hispanics ($545,795).[5] There were also gender differences, with women having lower per-person productivity losses ($401,046) than men ($441,903).

Taken together, these data demonstrate that melanoma is not only a physically devastating disease, but that it can also place a heavy economic burden both on the patients and society at large.

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GSK1120212 with chemotherapy (either dacarbazine or paclitaxel) in up to 297 patients with stage IIIc or stage IV malignant cutaneous melanoma (all having a BRAF mutation–positive tumor). This trial is not scheduled for completion until September 2012 (ClinicalTrials.gov Trial Number NCT01245062).

Vemurafenib. Developed by Plexxicon and Roche, this BRAF V600E inhibitor seems to be effective[18]—in some cases, dramatically effective—for patients with this mutation, though its effects seem to wane after a period of time.[19]

In previous studies, vemurafenib had induced response rates of 50% and more in patients with metastatic melanoma who have the BRAF V600E mutation. In the phase III BRIM3 study, this oral agent (960 mg bid) was compared with intravenous dacarbazine (1000 mg/m2 of body surface area) every 3 weeks as monotherapy in 675 previously untreated patients with stage IIIC or IV melanoma.

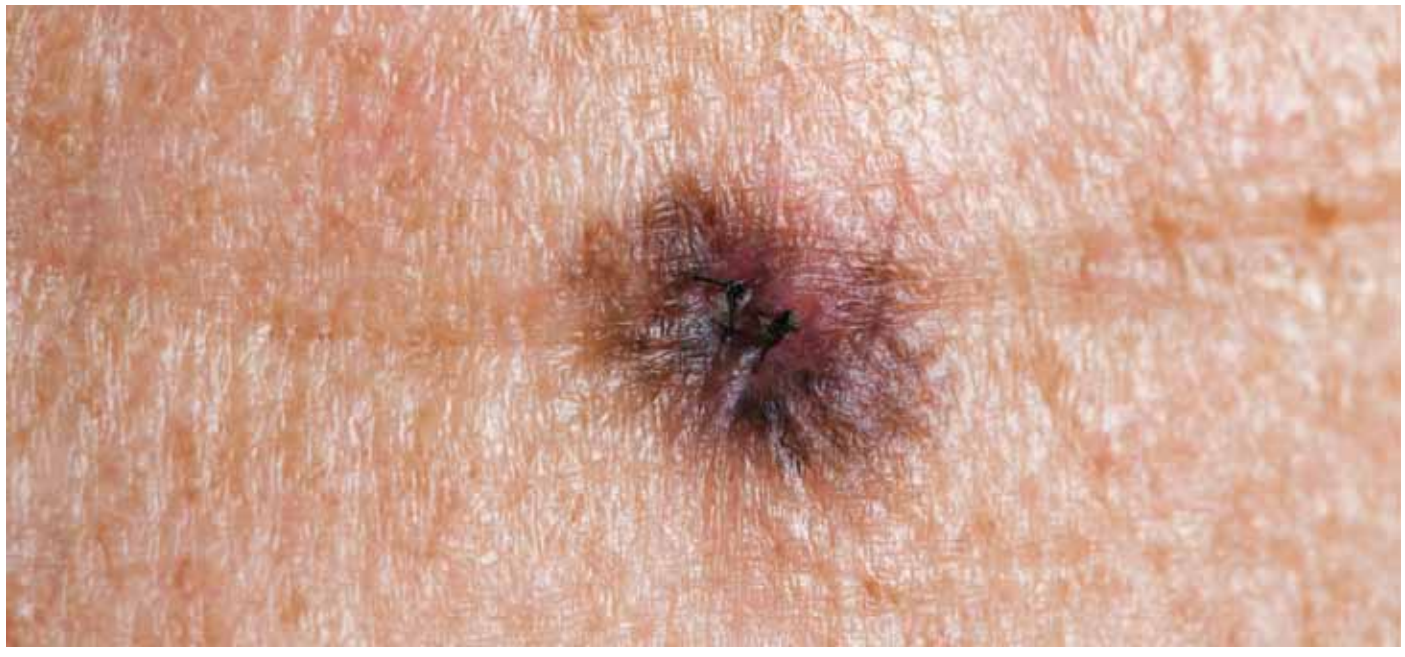
After 6 months of treatment, vemurafenib demonstrated an OS of 84% compared with 64% in the dacarbazine group. In the interim analysis for OS and final analysis for progession-free survival (PFS), vemurafenib demonstrated a 63% relative reduction in risk of death from melanoma compared with dacarbazine. Response rates were 48% for vemurafenib and 5% for dacarbazine (P <.001). In addition, the risk of the composite end point, death or disease progression, was 74% lower in the vemurafenib group (P <.001).[18]

However, this agent is not without significant side effects. Thirty-eight percent of the study population taking vemurafenib required dose adjustments to alleviate side effects such as photosensitivity skin reactions, arthralgia, and fatigue.[18]

Although this study did not report long-term follow-up, there is anecdotal evidence that patients who benefit from vemurafenib may not experience a recurrence for 7 months to 2 years or more.[19]

With the recent progress in treating metastatic melanoma using targeted therapies like ipilimumab and vemurafenib, might combination approaches of these 2 be next in line for clinical trials? Samjiv S. Agarwala, MD, at St. Luke's Cancer Center said, "Combination therapy would be an interesting research approach given the differences between ipilimumab (low response rate, prolonged duration) and vemurafenib (high response rate, possibly less durable)." Agarwala pointed out, however, that "Future trials with other agents in combination should address specific biomarkers."

A study to test this combination of vemurafenib and ipilimumab is listed on ClinicalTrials.gov but is not currently under way. Additionally, it is expected that the use of vemurafenib will be tested in coming years in a phase IIII study as adjunctive therapy in patients with metastatic melanoma.



Conventional Chemotherapy

There are few positive data to report on conventional chemotherapeutic agents in the treatment of metastatic melanoma. One of the few, tasisulam, has run into safety problems in phase III testing.

Tasisulam. Tasisulam is an acyl-sulfonamide compound which induces apoptosis through the mitochondrial-mediated cell death pathway. In phase II trials, 47% of patients taking tasisulam experienced some level of disease control, and a 2.6-month PFS (median) as second-line treatment of patients with unresectable or metastatic melanoma.[20] This was not a controlled trial. In December 2010, the SUMMIT-1 phase III registration trial of tasisulam versus paclitaxel stopped recruiting patients with metastatic melanoma because of 12 patient deaths that were potentially associated with the medication.[21] There is no further word from the manufacturer (Eli Lilly) whether dosing will be changed for continued enrollment or whether the trial has been discontinued permanently.

Conclusions

Although the late-stage pipeline for melanoma seems bustling, most of the interest is occurring around ipilimumab and vemurafenib, which have been approved for their initial indications.

The success of these 2 agents in treating metastatic melanoma may encourage more drug development activity for targeted therapy, according to Dr Agarwala. "I believe it will spur more drug development, as we are still a long way off from curing patients and the encouraging results seen so far have at least opened the door to even more effective drugs in the future," he remarked. "I believe the results with vemurafenib and ipilimumab are proof of principal trials that show these approaches are effective. Now let's move that up a notch and find drugs or combinations with even greater efficacy." **EBO**

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The Truth About Electronic Health Records

Why Oncologists Must Tailor Clinical Features to Their Needs

It's hardly shocking that physicians have generally resisted moving over to electronic health records (EHRs). Cost concerns and well-founded wariness over the lack of standards-based interoperability among many EHR systems has prevented many a doctor from making the leap.[1]

The problem is that healthcare information technology isn't going away. In fact, much like an aggressive disease, it's only going to grow stronger. Health reform and its ever-evolving changes are quickly transforming the EHR conversation from one of "I'll stick with paper" to "I'd best do this if I want my practice to be fully efficient."

The value gained from carefully researching and employing an EHR system is worth the investment, *especially* for oncologists, who are managing a gravely sick patient population.

The US Oncology Network is one of many oncology-based organizations that advocate for the use of healthcare information technology, encouraging physicians to embrace the array of benefits that lead to fewer errors, better targeted care and improved outcomes, access to vital life-saving treatments, and the latest research.[2]

Pick and Choose

The Oncology Electronic Health Record Field Guide,[3] a publication of the American Society of Clinical Oncology (ASCO), encourages oncologists to adopt an oncology-specific EHR rather than a generic one. For economic reasons, however, some oncology practices have opted for generic EHRs that have been tailored to their needs. But going this route carries the risk of not having the full menu of critical features that oncologists need. Plus, it's still likely that even oncology-specific EHRs will need to be customized within the subspecialties. For example, surgeons may not have much use for an EHR with a prescription-writing function because they typically prescribe only a handful of formulary medications for a limited amount of time, as opposed to medical oncologists whose chronically ill patients need multiple drugs. Each oncologist should pick and choose the functionalities they need, as laid out by ASCO:

- Tumor staging—Tumor-Node-Metastases (TNM) nomenclature and others
- Multidisciplinary and data-intensive work flow—pathology, lab, imaging
- Chemotherapy dosing and administration
- Toxicity assessment and management
- Clinical trial and protocol management
- Drug inventory management
- Survivorship care

Yet another benefit to employing an EHR is the fact that payers are giving closer attention to pay for performance (P4P). Knowing this, oncologists should be further encouraged to adopt the technology to ensure the efficient incorporation of consensus measures of quality and the use of best practice tools.

Add a Portal

Some EHRs include a patient portal application, enabling the physician to gather a patient's medical history before the first visit. With the portal, an individual's medical data can be directly uploaded into the EHR and become part of the permanent record.[3]

Additionally, with some systems, patients can establish and manage a separate personal health record (PHR), either as part of the EHR or as a separate Web-based tool. PHRs can store treatment history, making it simple for other medical facilities to capture and use the information.[3]

From a physician-to-physician standpoint, The US Oncology Network offers a Web-based community called "The Oncology Portal," which allows its member physicians to collaborate in real time.[3]

Case Study: Patient Portal

The following summary is from Navigating Cancer, Inc, an oncology-specific, HITECH-certified patient portal[4]:

Hematology Oncology Consultants, PA, is an established practice with 6 oncologists and 2 locations in the Orlando, Florida, region. They had not yet adopted an EHR and were looking for a solution that could help them achieve 3 goals:

- Offer their patients electronic access to their medical records and solve additional criteria to help them qualify for the federal HITECH Act Meaningful Use incentives.
- Begin capturing patient information in a structured database that had the flexibility to integrate with any future EHR vendor they selected.
- Find a cost-effective solution that would improve their new patient registration process while providing them with hard cost savings.

After implementing the patient engagement portal, the practice realized the following results:

- New patients register online from home, where they have access to their medical history, resulting in more complete and legible forms.
- Patient information now captured in a structured database, and once integrated with an EHR, will provide patients with access to their medical records online, both requirements to qualify for the Meaningful Use incentives.
- Patient education materials now delivered electronically, another requirement to qualify for the Meaningful Use incentives. Eliminated the need for paper materials, freeing up storage space in the clinic.
- Eliminated hard costs for printing and mailing new patient registration materials, saving $100 per doctor per month.
- High patient satisfaction, with 90% of patients agreeing or strongly agreeing that the online registration process was better than filling out paper forms.

Connect With Other Healthcare Organizations

Oncology reimbursement is changing as health reform continues to take shape. Bundled payments, episode-of-care payments, and, potentially, full capitation, are in the offing. To meet federal meaningful-use incentive targets, satisfy the data demands of health plan P4Ps, and participate in accountable care organizations (ACOs), it's important for oncologists to collaborate with other providers, hospitals, and insurers so that no one loses momentum during the transition.[7]

To expedite the process, oncologists should choose an EHR that's interoperable with other EHRs in their network. Talk to peers, physician referrers, and nearby hospitals to find out which EHRs they use. Also make sure that the EHR has interfaces to connect with those systems. If they don't, contact the vendor to find out how much the development costs will be. Connectivity between EHRs is the future and should be considered when deciding which one to choose.[5] **EBO**

Arm Yourself With Expert EHR Knowledge

The Oncology EHR Field Guide: Selecting and Implementing an EHR is a comprehensive, oncology-specific handbook developed to help practitioners select and implement current and future EHRs. Developed with input from volunteer oncologists, the 64-page book costs $76 for members and $95 for non-members. The following chapters are included:

- The Core Functions of an Oncology EHR
- Identifying the EHR Team and Beginning the Planning Process
- Building the Budget
- Making the EHR Selection
- Implementing the EHR
- Making the EHR Work for You
- Using the EHR to Support Quality of Care and Patient Safety
- Post-Implementation Ongoing Management

Source: Reference 6.

Even oncology-specific EHRs will need to be customized.

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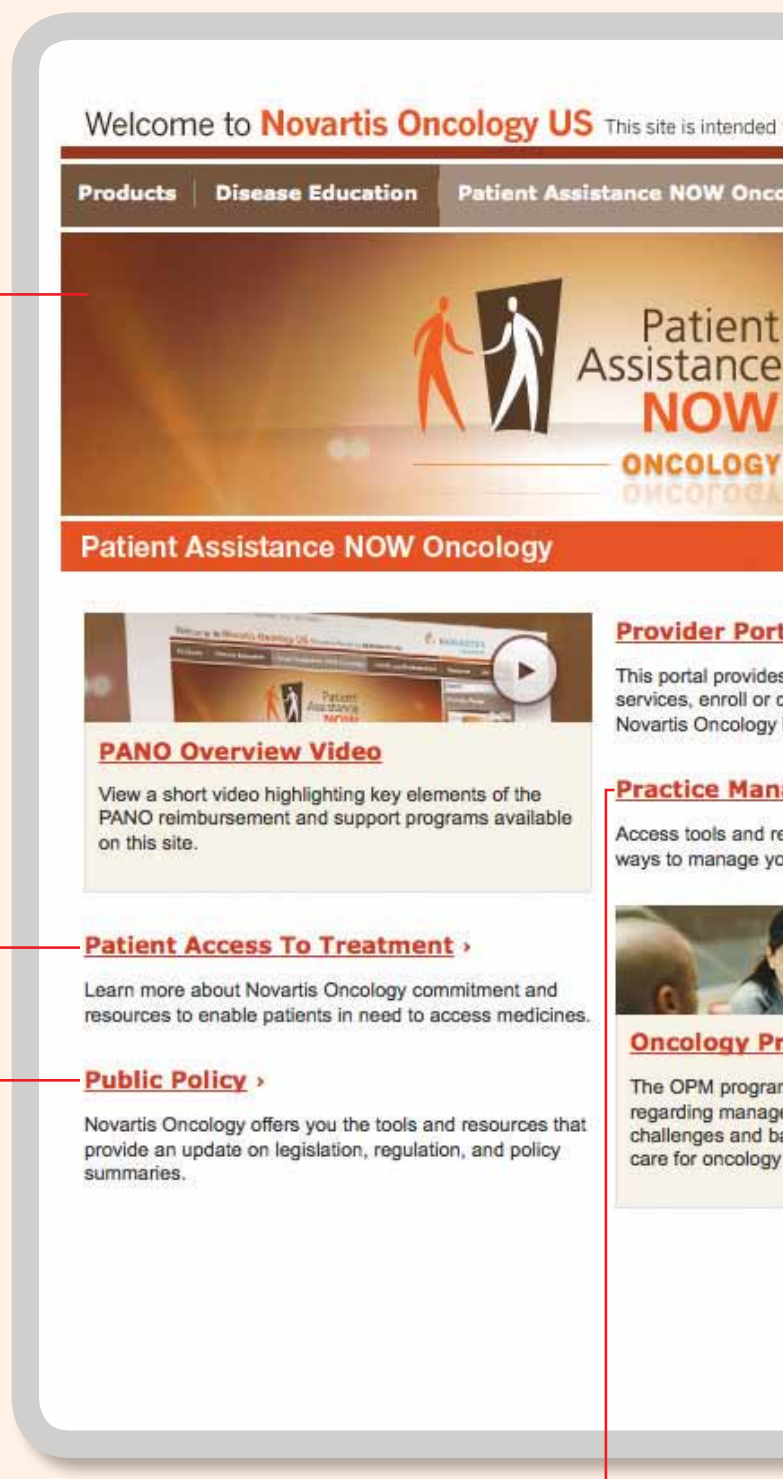

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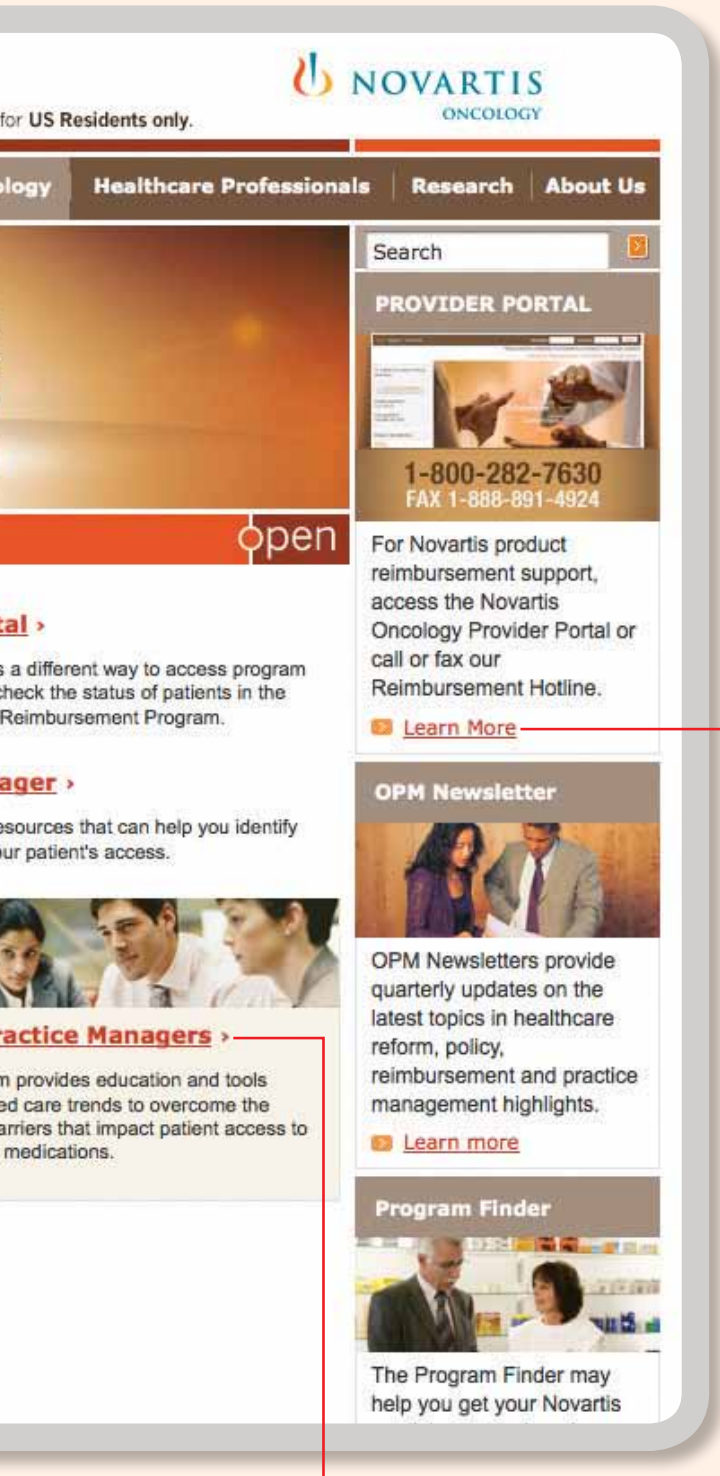

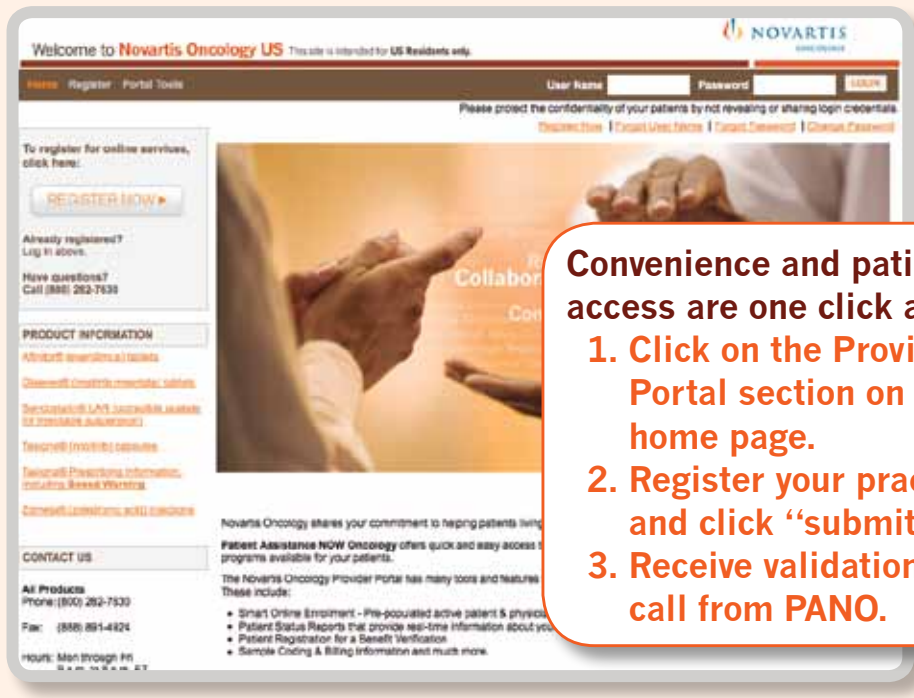

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The Great Biomarker Chase

Promise and Pitfalls Along the Path to Personalized Care

In recent years, the sequencing of the human genome and advances in supercomputer technology have helped drive hopes that a deeper understanding of the biology of cancer would yield the markers needed to truly usher in the long-awaited era of personalized medicine. While that optimism remains and there have been bright points of success, notable problems have slowed progress and led to criticism.

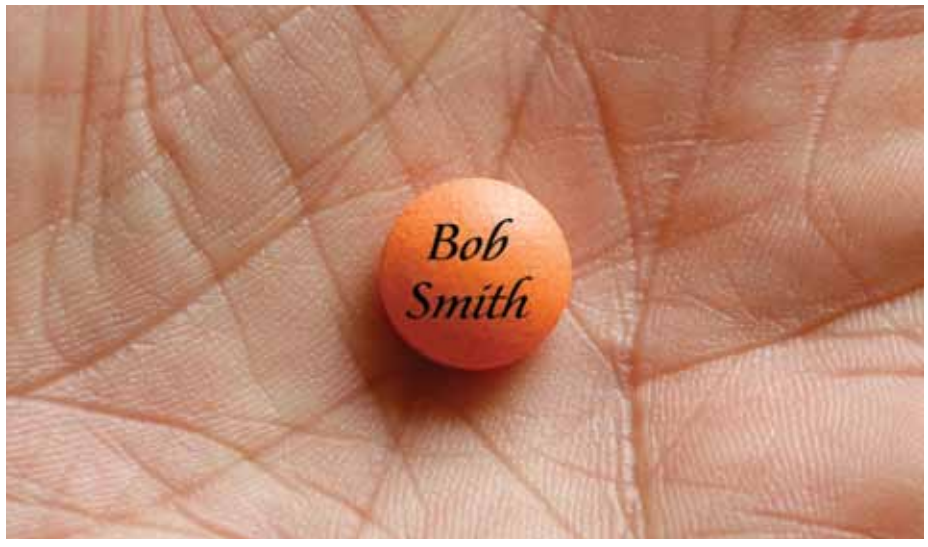
Biomarkers offer great potential for improving management of cancer at every point from screening and detection to diagnosis, staging, prognosis, and the assessment of treatment response. Striking advances have been made in several fields, particularly breast cancer, and fresh research suggests significant steps forward in lung cancer.

Currently, the Biomarkers Consortium, a public-private partnership founded by the Food and Drug Administration (FDA), the National Institutes of Health, and the pharmaceutical industry, is working on 9 projects, 2 of which are related to cancer. The Consortium is executing research into outcome measures for lung cancer and lymphoma, as well as a trial to "accelerate the pace of identifying effective novel agents for breast cancer."

Biomarkers are a large part of the personalized medicine movement. They are a tool to help doctors choose the right drug for the right patient. The use of biomarkers in studies can make it easier to determine whether or not an established treatment will work for specific patients with certain types of cancers.

If personalized medicine leads to a disease being detected at an earlier stage, the disease can be treated more effectively. But the use of biomarkers also means that doctors can reduce adverse drug reactions and shorten treatment by removing much of the uncertainty of trial and error. Furthermore, the use of biomarkers in personalized medicine can better aid preventative care by making it possible for doctors to predict who can get specific diseases by monitoring patients.

In clinical trials, biomarkers increase the efficiency of a drug trial by making it easier to eliminate potentially unsuccessful candidates early in the process. The ability of biomarkers to detect and monitor the progression of a disease can reduce the time span of drug discovery by as much as a decade, the FDA reported. According to the FDA, if a pharmaceutical company can increase its successful prediction of failure by even 10 percent, it could save easily $100 million. Yet progress has been slow on the vast, ever-changing, and controversial frontier of biomarker research, with fewer than 2 dozen cancer biomarkers approved so far by the FDA among the thousands researchers have explored.[1]



In August, the FDA approved 3 targeted therapies: an anaplastic lymphoma kinase inhibitor, an inhibitor of a mutation found in 40% to 60% of patients with cutaneous melanomas, and a drug for Hodgkin lymphoma patients who are CD30-positive.

Experts have advanced a brew of reasons for the gap between potential and performance, in a complex field that requires the coordination of a diverse team of pathologists, molecular biologists, and biostatisticians.

Last year, the AACR-FDA-NCI Cancer Biomarkers Collaborative described a "growing imperative" to modernize the drug development process, and made 27 recommendations in 8 different areas for doing so.[2] Meanwhile, the pharmaceutical industry is exploring ways to improve biomarker development, with some industry analysts seeing regulatory issues as a significant sticking point in economically feasible biomarker development (**Read More:** Industry Testing New Models for Developing Biomarkers).[3]

Sudhir Srivastava, PhD, MPH, the founding chief of the Cancer Biomarkers Research Group at the National Cancer Institute (NCI), said that one of the challenges in biomarker research is the unrealistic expectations promoted by many study investigators.

"With almost every paper, even if there is a remote chance of success, you see a press release hyping a discovery, but later on they fail," Srivastava said. "The public gets so excited about it that they demand we must succeed as soon as possible. But the fact of the matter is, the hype usually does not translate into clinical studies." At the same time, Srivastava said, the scientific community is getting organized and gaining momentum. "The infrastructure is in place to move forward in the right direction. More breakthroughs are a matter of time," he said.

"With almost every paper, even if there is a remote chance of success, you see a press release hyping a discovery, but later on they fail. The public gets so excited about it that they demand we must succeed as soon as possible. But the fact of the matter is, the hype usually does not translate into clinical studies."

—Sudhir Srivastava, PhD, MPH
Founding Chief
Cancer Biomarkers Research Group at the
National Cancer Institute

Notable Shortcomings Analyzed

Many researchers who have reviewed the progress made on biomarkers thus far have found much to criticize.

In 2010, Eleftherios P. Diamandis, MD, PhD, professor and head of the Division of Clinical Biochemistry, University of Toronto, Canada, and associate scientist at the Samuel Lunenfeld Research Institute of Mount Sinai Hospital, Toronto, reviewed cancer biomarkers initially hailed as breakthroughs and their subsequent failings.[4] These included nuclear magnetic resonance of serum for cancer diagnosis; lysophosphatidic acid for ovarian cancer; 4- and 6-parameter diagnostic panels for ovarian cancer; osteopontin for ovarian cancer; early prostate cancer antigen-2 (EPCA-2) for prostate cancer detection; proteomic profiling of serum by mass spectrometry for ovarian cancer diagnosis; and peptidomic patterns for cancer diagnosis.[4] Diamandis found problems ranging from inappropriate statistical analysis to biases in patient and control subject selection. Problems with EPCA-2, for example, included reporting values that were beyond the detection limit of the assay and using inappropriate agents to test EPCA-2.

Duke University recently gained the

national spotlight in one of the most widely publicized biomarker failings. A research team had devised genetic tests to assess tumor cells by looking for gene patterns that would determine which drugs would best attack a particular cancer. The tests turned out to be worthless, though they were once hailed as a breakthrough that was seen as the first fruit of the new genomics. The fact that the research relied on publicly available data sets and algorithms made it possible to determine it to be flawed. Keith A. Baggerly, PhD, and Kevin R. Coombes, PhD, statisticians at MD Anderson Cancer Center in Houston, Texas, spent 2000 hours finding all of the errors in the research and found even simple errors, such as row or column offsets.[5]

And at the NCI, the Cancer Biomarkers Research Group recently did its own random review of 1000 papers detailing biomarker discoveries. "In almost 90 percent of the papers, there was a lot of hype," Srivastava said.

Biomarker Successes Stand Out

Of course, there have been successes in the cancer biomarker field, one of the more significant biomarkers being the protein HER2. First discovered in the early 1980s, HER2 can be found in 20 to 25 percent of breast cancers, and an excess of this protein is found in some ovarian, stomach, lung, and uterine cancers. The excess production of HER2 causes tumors to grow faster and recur more frequently. The breast cancer drug trastuzumab (Herceptin) targets HER2, reduces its production, and even stimulates the body to attack cancers directly.

Another example is the Philadelphia chromosome, a marker for chronic myeloid leukemia, which results from the movement of DNA from one site on the human genome to another.

At the American Society of Clinical Oncology (ASCO) conference in June, featured research included a prospective study by the 14-member Lung Cancer Mutation Consortium that identified at least 1 of 10 "driver" mutations in tumors of nearly two-thirds of patients with advanced lung cancer.[6]

In a phase I trial, researchers from MD Anderson demonstrated that the ability to match individual patients with targeted cancer therapies based on the molecular profile of their tumors resulted in dramatically superior clinical outcomes, a finding that may improve patient selection for clinical trials at early stages and thus help speed drug development.[7]

In addition, researchers at Indiana University Melvin and Bren Simon Cancer Center in Indianapolis discovered the first predictive biomarker for taxane-induced peripheral neuropathy, single nucleotide polymorphisms in the RWDD3 gene, through a genetic analysis of more than 2000 breast cancer patients.[8]

The Cancer Biomarkers Research Group, which operates the Early Detection Research Network (EDRN), a collaborative effort of nearly 40 institutions, has a goal of accelerating the translation of biomarker information into clinical applications and evaluating new ways of testing tumors for predictive markers. "But we see our role as not just to be the accelerator of biomarker findings, but also to put the brake on bad findings," Srivastava said of the EDRN.

"If you use a test, there should be evidence that it is useful. We are trying to rein people in so they do not order so many tests when there is no meaningful evidence."

—Timothy D. Gilligan, MD
Oncologist
Solid Tumor Oncology Department
Cleveland Clinic

Key Hurdles Identified

Srivastava highlighted 3 key hurdles that have historically held back biomarker progress: a lack of foundational studies, a lack of sustained funding, and a lack of quality biological samples for testing. "The most important players in industry and the federal government are not investing enough, yet expectations are very high," he said. "If you look at the funding level for early detection and diagnosis, it is not as high as one would like to see as you do in drugs."

His budget is between $20 million and $26 million a year, spread out over about 40 institutions, which boils down to about $600,000 per institution. "It's not enough to do the discovery," he said, noting that investment in biomarkers may not be as appealing to investors because it is a long-term effort, while investors want to see short-term gains.

A lack of acceptable biological samples also has been a big obstacle, Srivastava and other scientists said. Many programs do not use quality samples, or there is not much information about the stage at which samples were collected.

Dean E. Brenner, MD, of the University of Michigan Medical Center, tackled this question during an ASCO presentation titled "An Update on Biomarkers for the Early Detection of Cancer, Prediction of Prognosis, and as Surrogate Endpoints for Cancer Prevention. "Garbage in, garbage out," he said, noting that biosamples can be unstable and difficult to analyze. "You need good quality."

Martin J. van den Bent, MD, PhD, Erasmus University Medical Center, The Netherlands, in a presentation on "Molecular Biomarkers in Neuro-oncology: Ready for Clinical Practice?" at the ASCO annual meeting, stressed the need for the adequate analytical performance of biomarkers, clinical performance, and independent validation. He cautioned that the biomarker research is still in need of development: "We need to think twice before we topple the old regime…. We could be looking at something so young and immature, the ugly ducklings that need to mature over time."

Moving Forward With Hope and Caution

None of the hurdles or the comparatively slow pace of progress mean it is time to give up hope, Srivastava said.

He said the most promising areas of cancer biomarker research over the next 5 years are prostate, ovarian, and colon cancers, and scientists are focusing more and more not just on single biomarkers, but on panels of biomarkers as successful diagnostic tools.

ASCO and other professional organizations are developing guidelines to help clinicians sort data regarding the usefulness of biomarkers in treating patients. Timothy D. Gilligan, MD, an oncologist in the Solid Tumor Oncology department at the Cleveland Clinic in Ohio, was part of an ASCO panel that developed guidelines on the appropriate uses for serum markers of germ cell tumors (GCTs).[9] The panel did an exhaustive search of published material, reviewing hundreds of papers to identify relevant studies, and developed consensus guidelines based on data from 81 reports.

Gilligan noted that GCTs are unique in that they are largely curable, even when they are very advanced, and that biomarkers have been used for a long time to measure tumor progression, with a fair amount of evidence supporting their use. "In almost all cases, when the marker goes up, it is a sign of the tumors progressing, and when the marker goes down, they are responding to treatment," he said. "There is a lot at stake in doing it right, though, so you don't overtreat people."

Like many other clinicians, Gilligan sees not only accuracy and reliability as big challenges with biomarkers, but also raises the question of utility. "Just because you can measure something doesn't mean it is helpful to measure," he said. "There are plenty of tumor markers that are often elevated if cancer is present, but knowing whether the marker is going up or down does not necessarily mean better care for the person."

"If markers go up 6 months before a scan goes up, is it helpful to start treatment 6 months earlier?" Gilligan asked. "In the vast majority of cases there [are] no data." Markers are most useful, he said, in diagnosing cancers where effective treatments exist.

In some cases like ovarian cancer, evidence suggests the earlier detection of a cancer antigen biomarker, CA125, does not help patients do better, Gilligan said. The flip side of the story, he said, is prostate-specific antigen (PSA), which is very sensitive. A rise in PSA does not necessarily impact wellness, or mean a man has prostate cancer, but Gilligan noted it often creates anxiety, with no consequences, and much time is spent reassuring patients. "There is a potential for markers to do harm."

He added, however, that new biomarkers that are more specific could be very useful in many areas. "If you use a test, there should be evidence that it is useful," he said. "We are trying to rein people in so they do not order so many tests when there is no meaningful evidence." **EBO**

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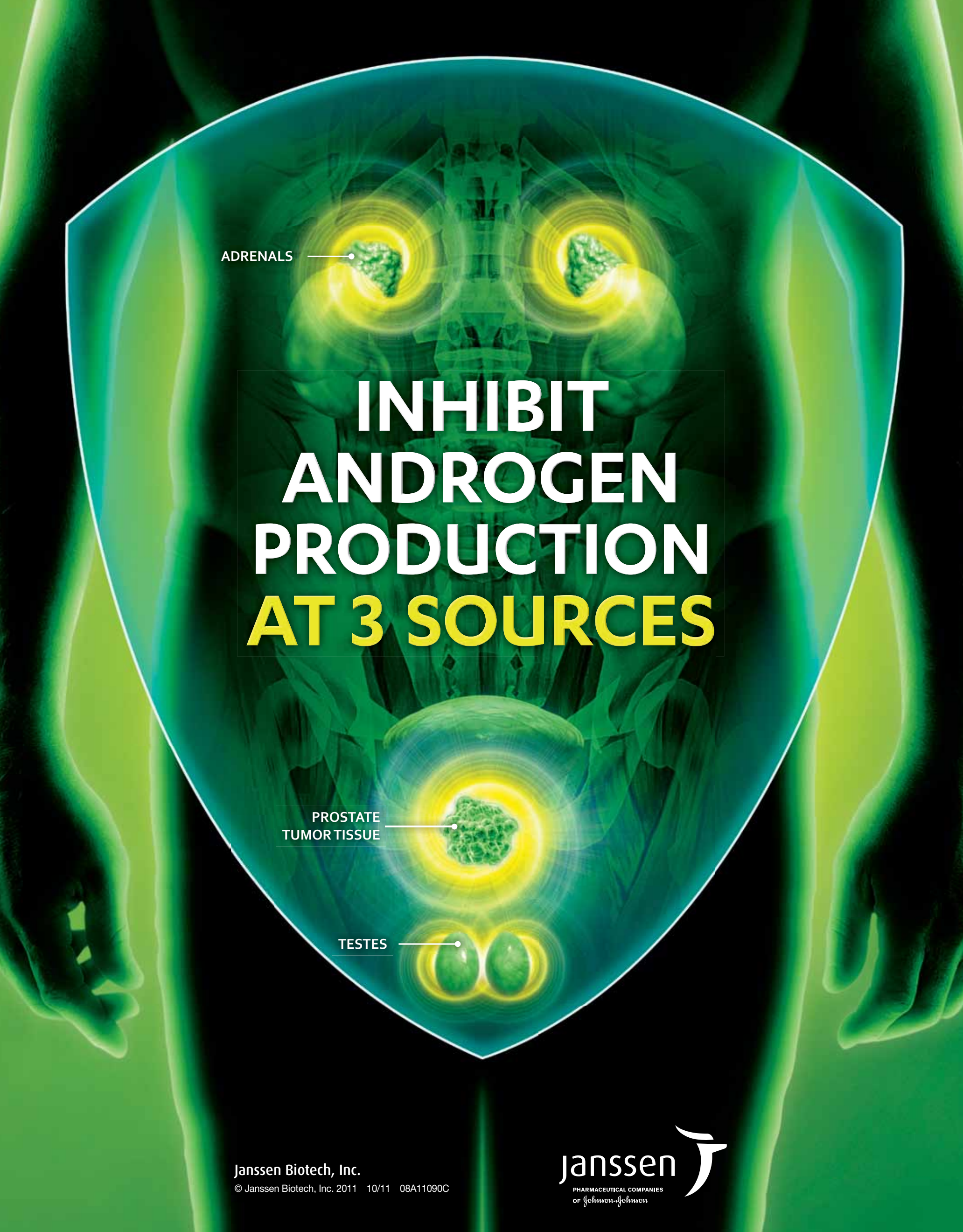

Janssen Biotech, Inc.

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

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THE AMERICAN JOURNAL OF MANAGED CARE

The 4 Pillars: Foundation for Care

The Duke Cancer Institute

Ongoing construction of the new cancer building at Duke, scheduled to open February 2012.

For more than 75 years, the cancer programs of Duke University Medical Center in Durham, North Carolina, have been at the forefront of research and patient care, with more than 800 researchers, physicians, and clinical staff serving nearly 6000 new patients each year from the United States and abroad. In 1972, Duke's cancer program was designated as one of the nation's 8 original comprehensive cancer centers by the National Cancer Institute (NCI), and is today one of only 40 such centers nationwide. Ranked as one of the top cancer hospitals in the United States for nearly 20 years by *US News & World Report*, Duke attracts the best cancer clinicians and scientists from across the country and around the world, and maintains clinical and research partnerships throughout the United States, as well as in India, China, and Singapore.

Those familiar with Duke's stellar reputation are well aware of the accolades, honors, and achievements credited to its cancer researchers, clinicians, and academicians, but few milestones have inspired the kind of excitement being generated by the November 2010 formation of the new Duke Cancer Institute (DCI). The DCI brings together clinicians, researchers, and educators from across Duke's hospital, medical school, and health system under a single administrative umbrella. This, in turn, intimately links patient care, research, and medical training in a unified pursuit. A new cancer center building is scheduled to open in February 2012, and a new leader, Michael B. Kastan, MD, PhD, was named to the Institute's helm in May.

Already, DCI promises to have a profound impact on both cancer research and patient care. By providing unprecedented and unique opportunities for teamwork between Duke's scientists and caregivers, the reorganization aims to more quickly translate novel therapies from bench to bedside and to optimize all aspects of patient care. The most important of its goals is to provide patients with a less tangible but equally critical tool in the battle against their cancers: hope. The Preston Robert Tisch Brain Tumor Center and the Duke Prostate Center (DPC) serve as 2 prime examples.

The Preston Robert Tisch Brain Tumor Center

Using the words "brain cancer" and "hope" in the same sentence may seem counterintuitive, but neuro-oncologist Henry S. Friedman, MD, co-director of the Preston Robert Tisch Brain Tumor Center, does so routinely and unabashedly.

"Everything we do for our patients is doomed to fail unless we're able to offer them hope," he said, "and the formation of the new Institute is helping to translate 'hope' from nebulous concept to concrete reality."

Established in 1937 as one of the nation's first brain tumor research and clinical programs, the Duke program was renamed the Preston Robert Tisch Brain Tumor Center in 2005 in recognition of a $10 million gift from the Tisch family. Today, the Center is one of the world's leading adult and pediatric neuro-oncology centers, and has received the NCI's highest rating of "outstanding" for each of the last 10 years.

The Center's 250-plus scientists, physicians, nurses, and other staff have at their disposal the resources of a leading research hub at the cutting edge of translational medicine, providing them with the means to offer patients the latest treatment advances, as well as access to a range of clinical trials, including those examining the efficacy of stem cell therapy and cancer vaccines. Equally important is the Center's reputation for providing the compassionate support needed by patients and their families living with brain and spinal cancers.

"The philosophy of hope has always formed the foundation for the care we provide at the Center," said Friedman, who considers brain and spinal cancers curable until proved otherwise. "This is a guiding principle that necessarily comes from the top down, and is continually nourished and sustained among veteran staff and new hires." He went on to note that, even for patients living with these most feared of all malignancies, the brain tumor center's integral role in the DCI fosters hope with an exchange of ideas and research findings that will speed the pace of discovery.

Friedman cited glioblastoma, the most common malignant brain tumor in adults, as an example. "While most people would tend to use the word 'hopeless' when referring to this diagnosis, patients with glioblastoma don't necessarily die, and many are living longer than ever before," he said. This point is borne out by NCI data showing that, compared with 1985, when fewer than 25% of patients lived 5 years with brain cancer, the 5-year survival rate now hovers at 35%, and more patients are surviving 10 and even 15 years past their initial diagnosis. (See http://seer.cancer.gov/faststats/selections.php?#Output.)

"Even those who ultimately succumb to their disease reap the benefits of enhanced quality of life," Friedman said. "Hope is self-sustaining." Friedman is, however, careful to differentiate between false hope and the hope given to patients at the Tisch Center. "We're not talking about some abstract concept based on hand-holding and words of encouragement," he stressed. "Real hope requires that we deliver substance."

The 4 Pillars

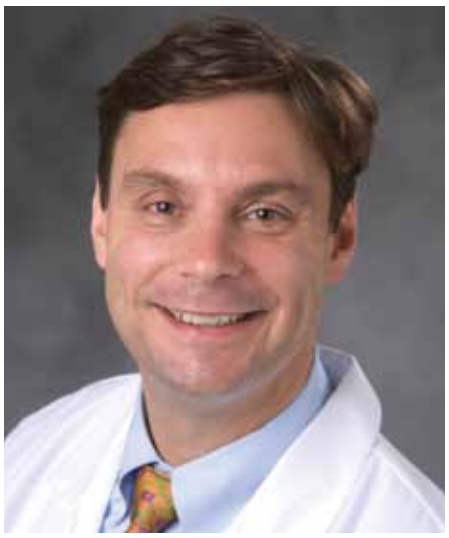
According to Friedman, "substantive hope" is one of the "4 pillars" that form the foundation for the care provided to the 900 to 1000 newly diagnosed patients seen each year at the Tisch Center. The other 3 core missions are basic research, clinical research, and exemplary patient care.

While the evaluation of a variety of therapeutic approaches is nothing new in the field of neuro-oncology, the care teams at the Tisch Center take this approach a step further by assessing the feasibility of multiple treatment strategies attempted not in sequence but all at once. "Rather than trying one treatment and then another when the first fails, we look at a comprehensive approach to treatment for each patient that may involve the use of multiple therapies from the onset," he explained.

Such an approach might involve approved therapies, along with those under investigation through clinical trials, including vaccines and targeted therapies involving monoclonal antibodies and anti-angiogenesis agents. The Center's researchers also are involved in comprehensive genetic analyses aimed at identifying tumor aberrations for targeting by these novel agents. "What the DCI does is foster a venue for the free flow of information among our scientists and clinicians," Friedman said. "There's little doubt that our patients will be the primary beneficiaries."

"Everything we do for our patients is doomed to fail unless we're able to offer them hope...and the formation of the new Institute is helping to translate 'hope' from nebulous concept to concrete reality."

—Henry S. Friedman, MD
Co-Director, Preston Robert Tisch Brain Tumor Center



"As successful as our cancer programs have been, the separation between research and clinical care has been somewhat limiting, and the new Institute is providing the means and venue for true continuity with respect to both research and patient care."

—Daniel J. George, MD
Director, Genitourinary Medical Oncology

Duke Brings Multidisciplinary Approach to Early Prostate Cancer Treatment

In 2004, the divisions of Urology and Medical Oncology and the department of Radiation Oncology at Duke University Medical Center instituted a special multidisciplinary clinic for patients with newly diagnosed prostate cancer. It drew together the 3 major players in prostate cancer treatment.

"Every Friday from 8:00 AM to 1:00 PM, a urologist, radiation oncologist, and medical oncologist get together to see patients," said Judd W. Moul, MD, FACS, director of the Duke Prostate Center. "It is one-stop shopping where the patient gets to see all 3 specialists in 1 visit."

Each physician sees 1 patient and does a standardized history and physical examination. The physicians then meet and discuss each patient at length. There are 2 more rounds so that all physicians see every patient. They usually have 2 sessions, running about 2 hours each, to see a total of 6 patients.

"We see patients who are mostly undecided about which treatment plan is the right one for them," said Moul. "This is a great option for the patients because they can see all 3 specialists and really get a thorough education on treatment options. They also get it all at once so they don't have time to forget what the radiation oncologist told them when talking to the urologist."

So far, more than 700 patients have been through the Clinic. The patients have consistently given it very high satisfaction ratings.

This is a very labor-intensive program, though, since the 3 physicians usually see only about 6 patients over a 5-hour block of time. It is largely focused on patient education, which is critically important in this group, but not supported well financially under the current system.

"The revenue generated during this time is very low compared to what these specialists could generate in regular practice," said Moul. "Healthcare institutions would generally be better off to have surgeons in the operating room, the radiation oncologists delivering treatments, and the medical oncologists seeing more patients during the allotted time. During the 5-hour block, an experienced clinician could have billed for 20 patient visits in a regular clinic or conducted 2 operations."

Currently the Clinic sees anyone who is interested. However, with all the changes in healthcare coming soon, Moul is concerned that this might not be affordable for the healthcare system much longer. Especially in a cohort that is largely Medicare.

Moul says they are currently looking at outcomes among clinic participants.

"Did those patients who went through the program have better outcomes?" he asked. "Because these patients received more intensive education and counseling, did they make better treatment decisions and have better survival?"

Another question they hope to answer soon is whether specific groups of patients may benefit more than others. It is possible that men with more aggressive cancers may have gotten better and more efficient treatment because all 3 major players were involved from the beginning.

"In the real world, most patients with low-risk, localized cancer will not see all 3 specialists," noted Moul. "From the payer standpoint, some may contend we may be driving up costs by requiring patients to see physicians that they don't need to. This is very much a work in progress and while we are proud of the work, we still have a lot to learn from this cohort of patients."

The first publication documenting outcomes from the multidisciplinary clinic will appear in the *Journal of Urology* in early 2012.

The Duke Prostate Center

Also receiving a new infusion of hope by virtue of DCI's reorganization are the patients of Duke's genitourinary cancer program, which has long been a leader among the specialties of Duke's cancer program.

Each year, Duke clinicians treat 700 to 800 newly diagnosed prostate cancer patients from around the world, and the number of those seeking treatment and/or second opinions at the DPC continues to grow. One favorable "side effect" of this growth is the recent influx of more than a dozen top medical oncologists, urologists, and radiation oncologists into the Duke program.

From the beginning, patients have had the opportunity to interact with a variety of specialists at the prostate cancer center, including urologists, medical oncologists, radiation oncologists, and support staff. But with the Center's scheduled move into the new clinical building in February, patients will have access to all prostate specialists under one roof in a facility that also will house many of the Center's scientists.

Urologist and medical oncologist Daniel J. George, MD, has been the director of the section of genitourinary medical oncology at Duke University Medical Center since 2003, and was recently appointed Duke's medical director of cancer clinical research.

"Our genitourinary cancer program serves as an excellent example of how and why the DCI will set Duke apart from other cancer centers," said George. "As successful as our cancer programs have been, the separation between research and clinical care has been somewhat limiting, and the new Institute is providing the means and venue for true continuity with respect to both research and patient care."

In what he described as a paradigm shift, George explained that the historically department based faculty has now become program based, with all resources pooled under the DCI umbrella. Also unique is the geographic proximity of the undergraduate campus to the medical center, facilitating collaboration between medical oncology, radiation oncology, pharmacology, and those from departments such as chemical engineering.

"It's an exciting time for genitourinary cancer researchers," said George, whose own research includes trials of drugs that inhibit blood flow to tumors and whose areas of interest include the study of blood flow in renal cell carcinoma and growth factors as prognostic markers and molecular targets in prostate cancer.

"We're now making very real strides in our understanding of the biology of these cancers, which, in turn, allows us to make some very meaningful progress," he said. George cited end-stage metastatic prostate cancer as a prime example, noting that, even in this late stage, the disease still appears to be testosterone-dependent. "This relatively new understanding has moved the field toward targeted therapies even in castrate-resistant disease," he explained, noting that ongoing research in areas such as upregulation of androgen and the use of copper-dependent agents to create conditional lethality is especially exciting.

Echoing George's enthusiasm is Stephen J. Freedland, MD, Duke's vice chief of urology research and associate director of genitourinary cancer clinical research. Freedland views the reorganization provided by the new Institute as a natural next step in the evolution of cancer care and research.

"The reorganization removes some significant barriers and allows us to take full advantage of our colleagues' areas of strength and expertise," he said. Freedland noted, for example, that clinical trials have historically tended to be a strength of medical oncologists, while urologists tended to excel at creating databases. The shared expertise made possible by the DCI will give Freedland access to the best of both worlds in his planned clinical trials to examine the effects of diet and lifestyle modifications on the progression of prostate cancer. He noted that it also will prove beneficial in his ongoing trial of the use of hormonal therapy in prostate cancer and a low-sugar diet for resultant diabetes.

Some clinics have already been

"We're all in this together. While many in the profession tend to give lip service to the terms 'teamwork' and 'multidisciplinary,' it's hard to imagine patient care, research, and even compensation being more intimately tied than here at Duke."

—Stephen J. Freedland, MD
Vice Chief, Urology Research
Associate Director, Genitourinary Cancer Clinical Research

THE AMERICAN JOURNAL OF MANAGED CARE

Duke University Medical Center Cancer Program Timeline

1930
Duke Hospital opens in Durham, NC.

1937
Duke establishes the nation's first brain tumor program.

1965
Duke establishes the nation's first physician assistant program.

1972
The Duke cancer program is designated as one of the original 8 comprehensive cancer centers by the National Cancer Institute.

1993
Duke physicians perform the first bone marrow transplant between an unrelated donor and recipient using blood salvaged from an umbilical cord.

2003
A national clinical trial led by Duke researchers is the first to show that a drug could shrink tumors by choking off their blood supply, leading to new weapons against brain tumors and other malignancies.

2005
Duke's brain tumor program is renamed the Preston Robert Tisch Brain Tumor Center.

2010
The Duke Cancer Institute (DCI) is formed to unite patient care, research, and learning under a shared mission.

2011
Michael B. Kastan, MD, PhD, formerly of St. Jude Children's Research Hospital, is named executive director of the DCI.

2012
A new 7-story, $220-million cancer building is scheduled to open at the heart of the hospital campus, adding 123 clinical rooms, 73 infusion stations, radiation oncology, and other services for outpatient care.

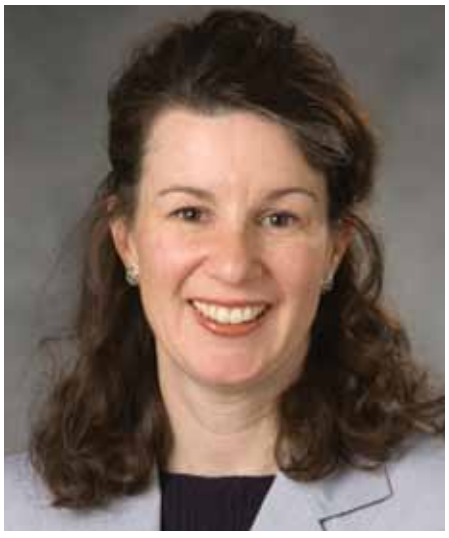
integrated, and Freedland noted that clinicians have begun to meet monthly to discuss patient care. "Everyone will have an equal voice and an equal stake in patient outcomes," he said, adding that even physician compensation will be determined by group productivity.

"We're all in this together," he said. "While many in the profession tend to give lip service to the terms 'teamwork' and 'multidisciplinary,' it's hard to imagine patient care, research, and even compensation being more intimately tied than here at Duke."

George agreed, citing the DCI as an example of the commitment to "break down barriers, pool resources, and live and die by the program's success."

George said that commitment is truly put to the test when patients are feeling especially desperate.

"It's especially inspiring to me when I see patients come from elsewhere with exhausted options and we're able to give those patients and their families a very real and concrete sense of hope," George said.



"With the integration of all facets of care into 1 physical and administrative setting, nurses will be working with new clinicians in new settings, and all will need to adjust to the realities of sharing and managing space and resources."

—Tracy K. Gosselin, RN
Associate Chief Nursing Officer

Nursing as the "Glue"

The rapid emergence of new therapies for both prostate and brain cancers has placed a renewed focus on the need for exemplary patient education and advocacy. "If we don't adequately explain the potential benefits and side effects of these new treatments, we run the risk of patients becoming noncompliant or simply giving up on treatment," said George. "And for those living with cancer as a chronic condition, patient education becomes a lifelong necessity," he added, acknowledging that nurses are often better than physicians at helping patients cope with the nuts and bolts of living with their cancer and the effects of therapy.

Tracy K. Gosselin, RN, Duke University Medical Center's associate chief nursing officer, noted that the new structure brought about by the DCI has shined a light on the need to examine the roles of nursing in a changing environment. "Many would describe nurses as the glue that ties together all the aspects of care for our patients," she said. Not surprisingly, education, advocacy, and symptom management are areas of critical importance. "To us, creating a weekly calendar of scheduled appointments or helping to translate the jargon of a consent form may seem routine, but to patients such things can actually make the difference between quitting and remaining on treatment," Gosselin said.

Challenges and Promise

With the opening of the new outpatient facility in 2012, both care and resources will be realigned, and Gosselin noted that the nursing care delivery model has been undergoing transformation for the past 18 months. "In our disease-based clinics, nurses have historically worked with specific physicians to treat specific cancers. With the integration of all facets of care into 1 physical and administrative setting, nurses will be working with new clinicians in new settings, and all will need to adjust to the realities of sharing and managing space and resources."

Such a change, said Gosselin, requires trust, and building trust takes time. "As we transition into the new building, nurses will be educated and reeducated, and every effort will be made to ensure that all feel part of the team."

Already, a retreat for nurses working in the DPC provided an opportunity to reexamine intake, clinic time, phone triage, and other issues that surfaced. Additionally, efforts are being made to align not just nurses and physicians but also social workers, dieticians, family and marital counselors, and other support staff in what amounts to a new configuration of care.

Also on Gosselin's short list of challenges is the nursing shortage and, in particular, finding ways to entice those with decades of frontline oncology experience to remain on staff or return post-retirement in a part-time or shift-work capacity. To this end, Gosselin stressed the importance of providing opportunities for continuing education, career trajectory, and other sources of professional satisfaction.

It is, said Gosselin, one of the great satisfactions of nursing to work with patients from diagnosis, through treatment, and on to long-term survivorship. Inherent challenges notwithstanding, she noted that the DCI promises to provide both the means and the opportunity for the collaborations that make such survivorship a reality. **EBO**

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Important Safety Information

Warnings and Precautions

FOLOTYN may suppress bone marrow function, manifested by thrombocytopenia, neutropenia, and anemia. Monitor blood counts and omit or modify dose for hematologic toxicities.

Mucositis may occur. If ≥Grade 2 mucositis is observed, omit or modify dose. Patients should be instructed to take folic acid and receive vitamin B_{12} to potentially reduce treatment-related hematological toxicity and mucositis.

Fatal dermatologic reactions may occur. Dermatologic reactions may be progressive and increase in severity with further treatment. Patients with dermatologic reactions should be monitored closely, and if severe, FOLOTYN should be withheld or discontinued.

Tumor lysis syndrome may occur. Monitor patients and treat if needed.

FOLOTYN can cause fetal harm. Women should avoid becoming pregnant while being treated with FOLOTYN and pregnant women should be informed of the potential harm to the fetus.

Use caution and monitor patients when administering FOLOTYN to patients with moderate to severe renal function impairment.

Elevated liver function test abnormalities may occur and require monitoring. If liver function test abnormalities are ≥Grade 3, omit or modify dose.

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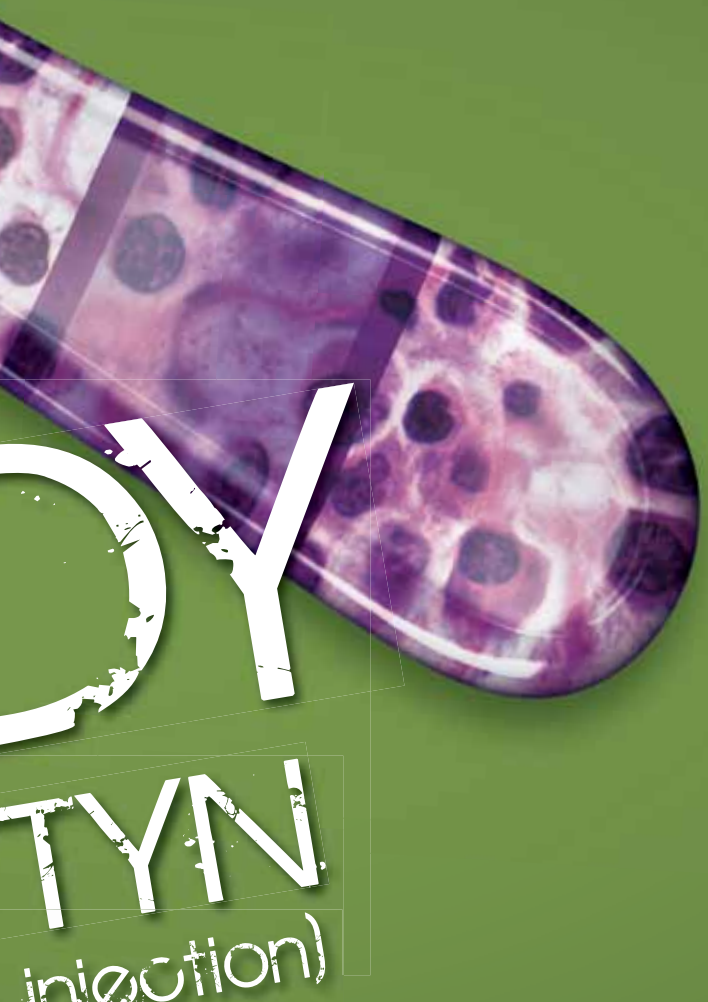
Please see accompanying brief

FOLOTYN is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. The indication for FOLOTYN is based on overall response rate. Clinical benefit such as improvement in progression-free survival or overall survival has not been demonstrated.



Adverse Reactions

The most common adverse reactions were mucositis (70%), thrombocytopenia (41%), nausea (40%), and fatigue (36%). The most common serious adverse events were pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea, and thrombocytopenia.

Use in Specific Patient Populations

Nursing mothers should be advised to discontinue nursing or the drug, taking into consideration the importance of the drug to the mother.

Drug Interactions

Co-administration of drugs subject to renal clearance (e.g., probenecid, NSAIDs, and trimethoprim/sulfamethoxazole) may result in delayed renal clearance.

Please see FOLOTYN Full Prescribing Information.

*Per independent central review

Demonstrated response in relapsed or refractory PTCL[1]

27% overall response rate (CR+CRu+PR) by independent central review (95% CI, 19-36)*

Of the responders,

66% responded within Cycle 1*

—Median time to first response was 45 days (range=37-349 days)

9.4-month median duration of response by central review (range=1-503 days)*

—12% (95% CI, 7-20) of patients had responses lasting ≥14 weeks (range=98-503 days)

Demonstrated response in

PROPEL—

the first large, prospective, single-arm, open-label clinical trial in PTCL

Reference: 1. FOLOTYN Prescribing Information. Allos Therapeutics, Inc., 2011.

FOLOTYN® (pralatrexate injection)

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summary of Prescribing Information.

Brief summary of Full Prescribing Information for FOLOTYN® (pralatrexate injection)—Please consult Full Prescribing Information.

INDICATIONS AND USAGE

FOLOTYN is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This indication is based on overall response rate. Clinical benefit such as improvement in progression-free survival or overall survival has not been demonstrated.

WARNINGS AND PRECAUTIONS

Bone Marrow Suppression

FOLOTYN can suppress bone marrow function, manifested by thrombocytopenia, neutropenia, and anemia. Dose modifications are based on ANC and platelet count prior to each dose.

Mucositis

Treatment with FOLOTYN may cause mucositis. If ≥Grade 2 mucositis is observed, omit dose and follow guidelines in Table 1.

Dermatologic Reactions

FOLOTYN has been associated with severe dermatologic reactions, which may result in death. These dermatologic reactions have been reported in clinical studies (14/663 patients [2.1%]) and post marketing experience, and have included skin exfoliation, ulceration, and toxic epidermal necrolysis (TEN). These reactions may be progressive and increase in severity with further treatment, and may involve skin and subcutaneous sites of known lymphoma. Patients with dermatologic reactions should be monitored closely, and if severe, FOLOTYN should be withheld or discontinued.

Tumor Lysis Syndrome

Tumor lysis syndrome has been reported in patients with lymphoma receiving FOLOTYN. Patients receiving FOLOTYN should be monitored closely and treated for complications.

Folic Acid and Vitamin B_{12} Supplementation

Patients should be instructed to take folic acid and receive vitamin B_{12} to potentially reduce treatment-related hematological toxicity and mucositis.

Pregnancy Category D

FOLOTYN can cause fetal harm when administered to a pregnant woman. FOLOTYN was embryotoxic and fetotoxic in rats and rabbits. 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.

Decreased Renal Function

Although FOLOTYN has not been formally tested in patients with renal impairment, caution is advised when administering FOLOTYN to patients with moderate to severe impairment. Monitor patients for renal function and systemic toxicity due to increased drug exposure.

Elevated Liver Enzymes

Liver function test abnormalities have been observed after FOLOTYN administration. Persistent liver function test abnormalities may be indicators of liver toxicity and require dose modification. Monitor patients for liver function.

ADVERSE REACTIONS

The most common adverse reactions observed in patients with peripheral t-cell lymphoma (PTCL) treated with FOLOTYN were mucositis, thrombocytopenia, nausea, and fatigue.

Clinical Trials Experience

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

The safety of FOLOTYN was evaluated in 111 PTCL patients in a single-arm clinical study in which patients received a starting dose of 30 mg/m^2 once weekly for 6 weeks in 7-week cycles. The median duration of treatment was 70 days (range 1-540 days).

Most Frequent Adverse Reactions

Table 4 summarizes the most frequent adverse reactions, regardless of causality, using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, version 3.0).

Table 4 Adverse Reactions Occurring in PTCL Patients (Incidence ≥10% of patients)

	N=111					
	Total		Grade 3		Grade 4	
Preferred Term	**N**	**%**	**N**	**%**	**N**	**%**
Any Adverse Event	111	100	48	43	34	31
Mucositis[a]	78	70	19	17	4	4
Thrombocytopenia[b]	45	41	15	14	21	19[b]
Nausea	44	40	4	4	0	0
Fatigue	40	36	5	5	2	2
Anemia	38	34	17	15	2	2
Constipation	37	33	0	0	0	0
Pyrexia	36	32	1	1	1	1
Edema	33	30	1	1	0	0
Cough	31	28	1	1	0	0
Epistaxis	29	26	0	0	0	0
Vomiting	28	25	2	2	0	0
Neutropenia	27	24	14	13	8	7
Diarrhea	23	21	2	2	0	0
Dyspnea	21	19	8	7	0	0
Anorexia	17	15	3	3	0	0
Hypokalemia	17	15	4	4	1	1
Rash	17	15	0	0	0	0
Pruritus	16	14	2	2	0	0
Pharyngolaryngeal pain	15	14	1	1	0	0
Liver function test abnormal[c]	14	13	6	5	0	0
Abdominal pain	13	12	4	4	0	0
Pain in extremity	13	12	0	0	0	0
Back pain	12	11	3	3	0	0
Leukopenia	12	11	3	3	4	4
Night sweats	12	11	0	0	0	0
Asthenia	11	10	1	1	0	0
Tachycardia	11	10	0	0	0	0
Upper respiratory tract infection	11	10	1	1	0	0

[a] Stomatitis or mucosal inflammation of the gastrointestinal and genitourinary tracts

[b] Five patients with platelets <10,000/μL

[c] Alanine aminotransferase, aspartate aminotransferase, and transaminases increased

Serious Adverse Events

Forty-four percent of patients (n=49) experienced a serious adverse event while on study or within 30 days after their last dose of FOLOTYN. The most common serious adverse events (>3%), regardless of causality, were pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea, and thrombocytopenia. One death from cardiopulmonary arrest in a patient with mucositis and febrile neutropenia was reported in this trial. Deaths from mucositis, febrile neutropenia, sepsis, and pancytopenia occurred in 1.2% of patients treated on all FOLOTYN trials at doses ranging from 30 to 325 mg/m^2.

Discontinuations

Twenty-three percent of patients (n=25) discontinued treatment with FOLOTYN due to adverse reactions. The adverse reactions reported most frequently as the reason for discontinuation of treatment were mucositis (6%, n=7) and thrombocytopenia (5%, n=5).

Dose Modifications

The target dose of FOLOTYN was 30 mg/m^2 once weekly for 6 weeks in 7-week cycles. The majority of patients (69%, n=77) remained at the target dose for the duration of treatment. Overall, 85% of scheduled doses were administered.

Post Marketing Experience

Toxic epidermal necrolysis has been identified during post approval use of FOLOTYN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure (*see Warnings and Precautions*).

DRUG INTERACTIONS

In vitro studies indicate that pralatrexate is not a substrate, inhibitor, or inducer of CYP450 isoenzymes and has low potential for drug-drug interactions at CYP450 isoenzymes. No formal clinical assessments of pharmacokinetic drug-drug interactions between FOLOTYN and other drugs have been conducted. The effect of co-administration of the uricosuric drug probenecid on pralatrexate pharmacokinetics was investigated in a Phase 1 clinical study. Co-administration of increasing doses of probenecid resulted in delayed clearance of pralatrexate and a commensurate increase in exposure.

Due to the contribution of renal excretion (approximately 34%) to the overall clearance of pralatrexate, concomitant administration of drugs that are subject to substantial renal clearance (eg, NSAIDs, trimethoprim/sulfamethoxazole) may result in delayed clearance of pralatrexate.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D (*see Warnings and Precautions*).

FOLOTYN can cause fetal harm when administered to a pregnant woman. Pralatrexate was embryotoxic and fetotoxic in rats at IV doses of 0.06 mg/kg/day (0.36 mg/m^2/day or about 1.2% of the clinical dose on a mg/m^2 basis) given on gestation days 7 through 20. Treatment with pralatrexate caused a dose-dependent decrease in fetal viability manifested as an increase in late, early, and total resorptions. There was also a dose-dependent increase in post-implantation loss. In rabbits, IV doses of 0.03 mg/kg/day (0.36 mg/m^2/day) or greater given on gestation days 8 through 21 also caused abortion and fetal lethality. This toxicity manifested as early and total resorptions, post-implantation loss, and a decrease in the total number of live fetuses. 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.

Nursing Mothers

It is not known whether pralatrexate 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 this drug, a decision should be made whether to discontinue nursing or to discontinue FOLOTYN, taking into account the importance of FOLOTYN to the mother.

Pediatric Use

Pediatric patients were not included in clinical studies with FOLOTYN. The safety and effectiveness of FOLOTYN in pediatric patients have not been established.

Geriatric Use

In the PTCL efficacy study, 36% of patients (n=40) were 65 years of age and over. No overall differences in efficacy and safety were observed in patients based on age (<65 years compared with ≥65 years).

No dosage adjustment is required in elderly patients with normal renal function.

Hepatic Impairment

Formal studies have not been performed with FOLOTYN in patients with hepatic impairment. Patients with the following laboratory values were excluded from the pralatrexate lymphoma clinical trials: total bilirubin >1.5 mg/dL; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 × upper limit of normal (ULN); and AST or ALT >5 × ULN if documented hepatic involvement with lymphoma.

Renal Impairment

See Warnings and Precautions.

OVERDOSAGE

No specific information is available on the treatment of overdosage of FOLOTYN. If an overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician. Based on FOLOTYN'S mechanism of action the prompt administration of leucovorin should be considered.

PATIENT COUNSELING INFORMATION

See FDA-approved Patient Package Insert.

Patients should be instructed to read the Patient Package Insert carefully.

DOSAGE AND ADMINISTRATION

FOLOTYN should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Peripheral T-cell Lymphoma

The recommended dose of FOLOTYN is 30 mg/m^2 administered as an intravenous (IV) push over 3-5 minutes via the side port of a free-flowing 0.9% Sodium Chloride Injection, USP IV line once weekly for 6 weeks in 7-week cycles until progressive disease or unacceptable toxicity.

Vitamin Supplementation

Patients should take low-dose (1.0-1.25 mg) oral folic acid on a daily basis. Folic acid should be initiated during the 10-day period preceding the first dose of FOLOTYN, and dosing should continue during the full course of therapy and for 30 days after the last dose of FOLOTYN. Patients should also receive a vitamin B_{12} (1 mg) intramuscular injection no more than 10 weeks prior to the first dose of FOLOTYN and every 8-10 weeks thereafter. Subsequent vitamin B_{12} injections may be given the same day as treatment with FOLOTYN (*see Warnings and Precautions*).

Monitoring and Dose Modifications

Management of severe or intolerable adverse reactions may require dose omission, reduction, or interruption of FOLOTYN therapy.

Monitoring

Complete blood cell counts and severity of mucositis should be monitored weekly. Serum chemistry tests, including renal and hepatic function, should be performed prior to the start of the first and fourth dose of a given cycle.

Dose Modification Recommendations

Prior to administering any dose of FOLOTYN:

- Mucositis should be ≤Grade 1.
- Platelet count should be ≥100,000/μL for first dose and ≥50,000/μL for all subsequent doses.
- Absolute neutrophil count (ANC) should be ≥1,000/μL.

Doses may be omitted or reduced based on patient tolerance. Omitted doses will not be made up at the end of the cycle; once a dose reduction occurs for toxicity, do not re-escalate. For dose modifications and omissions, use the guidelines in Tables 1, 2, and 3.

Table 1 FOLOTYN Dose Modifications for Mucositis

Mucositis Grade[a] on Day of Treatment	Action	Dose upon Recovery to ≤Grade 1
Grade 2	Omit dose	Continue prior dose
Grade 2 recurrence	Omit dose	20 mg/m^2
Grade 3	Omit dose	20 mg/m^2
Grade 4	Stop therapy	

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

Table 2 FOLOTYN Dose Modifications for Hematologic Toxicities

Blood Count on Day of Treatment	Duration of Toxicity	Action	Dose upon Restart
Platelet <50,000/μL	1 week	Omit dose	Continue prior dose
	2 weeks	Omit dose	20 mg/m^2
	3 weeks	Stop therapy	
ANC 500-1,000/μL and no fever	1 week	Omit dose	Continue prior dose
ANC 500-1,000/μL with fever or ANC <500/μL	1 week	Omit dose, give G-CSF or GM-CSF support	Continue prior dose with G-CSF or GM-CSF support
	2 weeks or recurrence	Omit dose, give G-CSF or GM-CSF support	20 mg/m^2 with G-CSF or GM-CSF support
	3 weeks or 2nd recurrence	Stop therapy	

Table 3 FOLOTYN Dose Modifications for All Other Treatment-related Toxicities

Toxicity Grade[a] on Day of Treatment	Action	Dose upon Recovery to ≤Grade 2
Grade 3	Omit dose	20 mg/m^2
Grade 4	Stop therapy	

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

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Rev.3: January 2011

Nab-Paclitaxel *(Abraxane)*

Nab-paclitaxel (Abraxane) is an alternative form of the drug where paclitaxel is bound to albumin nanoparticles.

It is an antimicrotubule agent. These work to inhibit the microtubule structures, a part of the cell's machinery for replicating itself. Inhibition of these structures ultimately results in cell death.

Paclitaxel usually requires solvents to dissolve it before the medication can be administered. When bound to albumin, it dissolves more readily, negating the need for irritating solvents. This means that the medication can be injected more quickly than the non-bound version. There are also indications that the nab-paclitaxel version may preferentially enter the cell.[1,2]

Nab-paclitaxel is indicated for use in the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.[3]

The economic impact of nab-paclitaxel has been mixed. Dranitsaris and colleagues looked at clinical and safety data comparing it with docetaxel and noted that nab-paclitaxel had the lowest incidence of grade 3-4 toxicity and lower overall costs of managing the toxic effects. When they used the median number of cycles given and the cost effects of the toxicity, overall cost for nab-paclitaxel was $15,105 compared with $15,268 for docetaxel and $3357 for paclitaxel. However, the incremental cost per quality-adjusted life-year (QALY) gained was more favorable for nab-paclitaxel than docetaxel ($56,800 vs $739,600).[4]

Another study by the same group compared nab-paclitaxel weekly or every 3 weeks with a standard regimen of docetaxel. Patients getting nab-paclitaxel 100 mg/m2 weekly and 300 mg/m2 every 3 weeks had average costs comparable to the docetaxel arm. Those administered nab-paclitaxel 150 mg/m2 weekly had significantly higher overall costs, but also had a significant improvement in progression-free survival. Relative to docetaxel, the incremental costs per progression-free year were £5660, £31,800, and £9900 for the 100 mg/m^2 weekly, 150 mg/m^2 weekly, and 300 mg/m^2 every 3 weeks dosing, respectively.[5]

Lenalidomide *(Revlimid)*

Lenalidomide (Revlimid) in combination with dexamethasone is indicated for the treatment of multiple myeloma (MM) patients who have received at least 1 prior therapy.

How lenalidomide works is not well understood. Experiments have demonstrated that lenalidomide inhibits the growth of cells derived from patients with multiple myeloma in vitro. It has been shown to inhibit the secretion of pro-inflammatory cytokines such as tumor necrosis factor alpha. Lenalidomide also inhibited the expression of cycoloxygenase-2 (COX-2) but not COX-1 in vitro.[6]

A study by Fullerton et al assessed resource utilization in MM associated with 4 approved therapies. They included single-agent bortezomib, bortezomib with pegylated liposomal doxorubicin, thalidomide plus dexamethasone, and lenalidomide plus dexamethasone in their models.

The costs in all models were primarily driven by the direct expenditures for the drugs. The $64,806 cost for lenalidomide with dexamethasone was a 1.7-fold increase over the combination including thalidomide, and a 1.9-fold increase over drug costs for the bortezomib/doxorubicin combination.

Adding associated medical costs to the model, lenalidomide/dexamethasone represented a cost savings compared with the other regimens. The total cost, including prophylaxis for deep vein thrombosis and pulmonary embolism, was 1½ times that seen in either the thalidomide/dexamethasone or the bortezomib/doxorubicin combination.[7]

A discrete event simulation model was used to estimate long-term health and cost results of lenalidomide plus dexamethasone versus dexamethasone alone in patients with MM who had received either 1 or 2 or more prior rounds of therapy.

In those with just 1 prior therapy, lenalidomide with dexamethasone was associated with improvements in both survival and QALYs when compared with dexamethasone alone. They equated this to £20,617 per life-year gained and £28,943 in QALYs gained in those patients who received lenalidomide.

When the group with 2 or more previous therapies was assessed, similar results were seen. The incremental cost of the combination was £19,218 per life-year gained and £28,184 per incremental QALY gained.[8]

Ipilimumab *(Yervoy)*

Ipilimumab (Yervoy) is indicated for use in melanoma that has metastized or cannot be removed by surgery. It is a recombinant, human monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4).

Blockade of CTLA-4 augments T-cell activation and proliferation. The mechanism of action of ipilimumab in patients with melanoma is indirect, possibly through a T-cell mediated anti-tumor immune response.[9]

Because of its relative newness, having been approved by the FDA in March 2011, the economic impact of ipilimumab is not yet well defined. A Medline search using the drug's name and the MESH terms "cost-benefit analysis" and "drug cost/statistics and numerical data" found no studies. A more general search using Google was similarly unproductive, returning only a draft report by England's National Institute for Clinical Excellence (NICE) and a similar one from Ireland's National Centre for Pharmacoeconomics (NCPE).

NICE tentatively recommended against adding ipilimumab to the National Health System's coverage. This does not mean that the medication will be banned, just that the governmental program will not pay for treatment.

The Committee concluded that the most plausible cost per year of improved health would fall between £54,000 and £70,000 per QALY gained. They did note that a lack of data on longer-term benefits could result in a significantly higher true incremental cost-effectiveness ratio (ICER).[10]

The NCPE also completed an economic evaluation of the medication. The Centre looked at a Markov decision analysis indicating a baseline incremental cost per QALY gained with ipilimumab versus best supportive care as €147,899. The incremental cost per life-year gained was €92,443.

A probabilistic sensitivity analysis indicated that the probability of ipilimumab being cost-effective over a willingness to pay range between €20,000 per QALY to €45,000 per QALY was 0%.

The budget impact assessment, based on a cost per dose above €20,000 and an average cost of treatment over 4 cycles, exceeded €85,000. Differing scenarios put the gross budget impact of using the medication between €4.8 million and €7.4 million in 2012. This would have increased between €500,000 and €1.8 million by 2016.

This led the Centre to conclude that there had been a failure "to demonstrate the cost-effectiveness of ipilimumab for the treatment of advanced melanoma in adult patients who received prior therapy."

Because of that, the Centre could not recommend reimbursement at the submitted price.[11] **EBO**

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THE AMERICAN JOURNAL OF MANAGED CARE

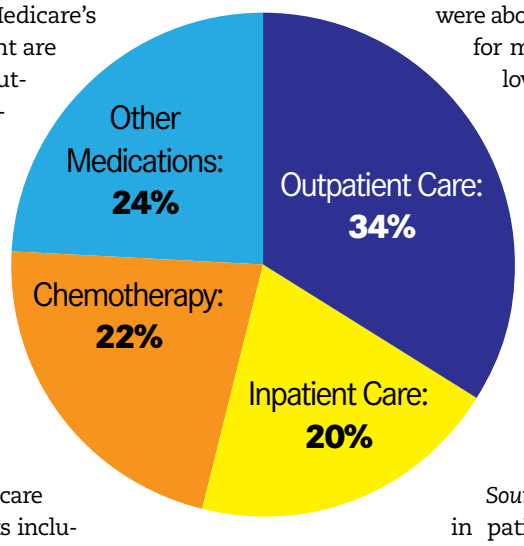
LUNG CANCER

Where Are We Spending the Most Money in Metastatic Lung Cancer?

Metastatic lung cancer is frequently diagnosed and extremely difficult to treat; a great deal of resources are expended on therapies and health services for patients with metastatic lung cancer once they undergo chemotherapy. In 2004, lung cancer treatment expenditures were one-fifth of Medicare's entire spending on cancer. The benefits of lung cancer treatment are limited, and therefore therapy costs must be weighed against outcomes. This is particularly true today, as there is increased scrutiny on the costs of care—even cancer care.

Researchers from Amgen, Kaiser Permanente, and the health economic consultant Policy Analysis Inc studied the health claims of 4068 patients (mean age, 65 years) who began chemotherapy between 2000 and 2006 until their deaths or the end of the study period to determine cumulative healthcare resource utilization and expenditures. The information was collected from a large, private, multi-payer health insurance claims database. Patients' inpatient and outpatient service claims and medication claims were followed for a median of 334 days.

Over a mean 500-day follow-up period, the cumulative healthcare expenditures averaged $125,849 per patient. Total healthcare costs included 34% for outpatient care, such as emergency department and/or physician office visits, hospital outpatient/home health/hospice/skilled nursing services, and 20% for acute hospital inpatient care. Outpatient chemotherapy and other medication costs were estimated at 22% and 24%, respectively (Figure). For patients whose total costs were above $200,000, chemotherapy and other medication costs accounted for more than 50% of the total, percentages similar to those with far lower total costs.



The majority of costs for patients with metastatic lung cancer receiving chemotherapy are associated with outpatient and not inpatient care, the researchers pointed out. This may be important, they added, when allocating overall healthcare resources, identifying possible cost savings from disease prevention, and assessing the cost-effectiveness of new medical interventions. Cost-effectiveness evaluations of new strategies for preventing, screening, and treating early stage and metastatic lung cancer can be useful when regulatory and reimbursement decisions must be made, according to the researchers.

Source: Vera-Llonch M, Weycker D, Glass A, et al. Healthcare costs in patients with metastatic lung cancer receiving chemotherapy. *BMC Health Services Research*. 2011;11:305.

OVARIAN CANCER

Treatment Response and Survival in Patients With Epithelial Ovarian Cancer

Interest in the use of biomarkers has grown to help determine which patients have a greater likelihood of receiving optimal benefit from oncologic treatments. This concept of optimizing the value of treatment is now being applied to another aspect of cancer care. Investigators from the University of Minnesota used mathematical modeling to help determine whether global gene expression data of tumor tissue attained during surgery and before the beginning of chemotherapy treatment in 54 patients with advanced stage epithelial ovarian cancer (EOC) can help predict which patients would mostly likely suffer a recurrence.

The researchers developed 3 prognostic biomarker models (termed F1, F2, and F3) based on the existence of tumor gene combinations (from a total of 12 genes) that were very accurate (overall sensitivity: 96%–100% and overall specificity: 96%–100%) in identifying both the patients who responded (long-term survivors [LTS]) and the non-responders (short-term survivors [STS]) to platinum/taxol chemotherapy. From a total population of 54 individuals, the researchers randomly selected 34 patients (14 LTS, 20 STS) in order to develop and test the F_1, F_2, and F_3 prognostic biomarker models. This discovery study phase was the first step in assessing a prognostic (or a diagnostic) test, resulting in extremely high sensitivity and specificity. In the validation study, information from the tumors of 20 patients (not included in the discovery phase) were used to test the 3 prognostic biomarker models. In this phase, all 3 models gave a correct prognosis for the 20 unknown subjects with regard to treatment response and survival.

When the discovery study and validation study results were then combined, the F1 and F3 models had a treatment response sensitivity of 100% (24/24 LTS subjects) and a specificity of 97% (29/30 STS subjects). The F2 model demonstrated a sensitivity of 96% (23/24 LTS subjects) and a specificity of 1.000 (30/30 STS subjects). In terms of survival, both the F1 and F3 models demonstrated a sensitivity of 97% (29/30 STS subjects) and a specificity of 100% (24/24 subjects), whereas the F2 model had perfect sensitivity (30/30 STS subjects) and a specificity of 96% (23/24 subjects).

The 12 tumor genes tested were categorized into 3 general groups: (1) genes that regulate cytostructural protein expression, (2) genes for cell proliferation regulation, and (3) metabolism regulation genes.

By using these prognostic biomarker tests to develop new, more effective pharmacological regimens, the researchers noted, considerably more successful treatments and a significant increase in survival rates for all patients with advanced stage EOC are possible.

Source: Nikas JB, Boylan KLM, Skubitz APM, Low WC. Mathematical prognostic biomarker models for treatment response and survival in epithelial ovarian cancer. *Cancer Informatics*. 2011:10;233-247.

MULTIPLE MYELOMA

A "Poster Child" for Targeted Cancer Therapy?

Multiple myeloma (MM) exhibits considerable biologic and clinical variation—it is not surprising, then, that a single, uniform therapeutic approach for patients with MM fails more often than it succeeds, said commentators from the University of Texas MD Anderson Cancer Center, Houston, and Changzheng Hospital, Shanghai, China.

Much work had gone into developing a 70-gene and 15-gene model, created by the University of Arkansas for Medical Sciences (UAMS) and the Intergroupe Francophone du Myelome, respectively, to identify patient populations who are at risk of poor outcomes as determined by their tumor gene expression profiles (GEPs). Effective as well as distinct treatments for different MM subtype patients that improved response rate, progression-free survival, and overall survival with low toxicity and rational cost-effectiveness was the ultimate aim of the stratification.

Total therapy 4 (TT4) by UAMS and Mayo Stratification of Myeloma Risk-Adapted Therapy consensus guidelines from the Mayo Clinic are 2 typical examples of targeted therapy, based on the GEP stratifications. A 2-year complete response will be the primary clinical end point of ongoing research to determine the validity of guidelines. Mayo Clinic researchers categorized patients into standard-risk, intermediate-risk, and high-risk groups depending on mutations and abnormalities discovered through multiple methods. Sixty percent were standard risk, and 20% of patients were determined to be in the high- and low-risk groups. Personalized therapy recommendations included regimens that could result in a high overall response rate with minimal early toxicity for a standard-risk patient. Those in the intermediate-risk group could follow a bortezomib-based induction regimen (high-dose melphalan) with or without consolidation before lenalidomide maintenance. The authors pointed out that in the high-risk subjects, new drugs and novel approaches may be best, and a "total therapy 3 like" approach may be most appropriate for patients exhibiting p53 deletion.

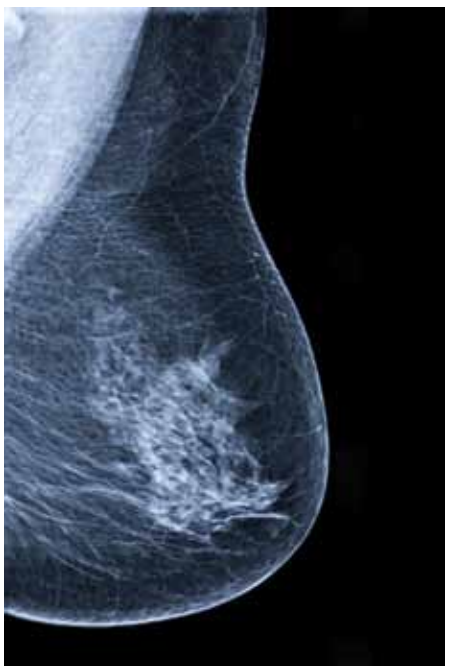
Although there are now over 40 novel pharmacologic targets presently undergoing clinical trials, the authors acknowledged that it is still not clear which will play a critical role for any subgroup of patients with multiple myeloma. Strengthening the insights on patient stratifications according to molecular heterogeneity and making rationally cost-effective treatment available for different subsets of patients should be the goal, they noted, and can be achieved by optimizing the current therapeutic strategies. A particular emphasis should be placed on immunomodulatory therapies, the authors concluded, because of their potential to eliminate remaining myeloma cells that will enhance the efficacy after a bone-marrow transplant.

Source: Jiang H, Yi Q, Hou J. Strategic consideration on treatment of multiple myeloma (editorial). *Chin Med J*. 2011;124:2965-2968.

BREAST CANCER

Developments in Treatment Approaches to Patients With HER-2+ Breast Cancer Refractory to Trastuzumab

Before the introduction of trastuzumab in the 1990s, women with breast tumors overexpressing the human epidermal growth factor receptor (HER)-2 gene had significantly shorter survival than patients found to be negative for HER-2 overexpression. The advent of targeted therapy with trastuzumab was touted as one of the first successes in matching molecular biomarkers with effective pharmacologic treatment. Overall survival in patients receiving this monoclonal antibody in addition to chemotherapy had an overall survival that was 5 months longer than those who did not receive the combination as first-line therapy. However, more than 50% of women with advanced breast cancer exhibit resistance to trastuzumab, and disease progression and/or recurrence is common in those who originally respond to therapy.



Oncologists from China and the United Kingdom sought to review the mechanisms of resistance and find new ways of classifying molecular pathways that would identify biomarkers, enabling additional methods for effectively stratifying patients who will benefit more fully from trastuzumab treatment. They categorized the possible causes for resistance to trastuzumab as follows:

1. Expression of p95HER-2, an abbreviated form of HER-2 that does not possess the binding receptor to which trastuzumab attaches
2. Activation of the PI3K-AKT pathway (in a small retrospective study, patients demonstrating activation of this pathway had poor response to treatment)
3. Abnormal signaling of other receptors, such as HER-3, insulin-like growth factor 1 receptor, and EGFR
4. Other miscellaneous mechanisms, such as expression of glycoprotein mucin 4 and autocrine production of transforming growth factor-beta

Much work is ongoing to find medications that are useful in patients with trastuzumab resistance, which work against 1 or more of these pathways. For example, lapatinib's response rates as monotherapy are very low (up to around 5%). Response rates in combination with other chemotherapy does exhibit differences in time to disease progression of about 2 months. Multi-HER tyrosine-kinase inhibitors are currently in clinical trials that show some promise in trastuzumab-resistant patients, helping about one-fourth of patients in a phase 2 trial.

The authors also pointed out that more research is needed to clarify the molecular mechanisms differentiating trastuzumab-resistant and –refractory breast cancer. It may also be that this intensive research reveals that resistance may be less frequent with another monoclonal antibody related to trastuzumab, like neratinib, and that this should be used eventually as first-line therapy.

They concluded that the financial resources needed to pay for targeted agents requires that we know a good deal more about the molecular pathways from which resistance to these therapies may develop. In other words, the situation is not so simple: a targeted therapy may be found and seems to be a substantial improvement over previous treatments. Challenges, such as resistance, may complicate the financial equation, and will drive more research into biomarkers of resistance, possibly to target the reason for resistance. Could that mean targeted therapy to help those resistant to the original targeted agent?

Source: Wong H, Leung R, Kwong A, et al. Integrating molecular mechanisms and clinical evidence in the management of trastuzumab resistant or refractory HER-2$^+$ metastatic breast cancer. *The Oncologist*. 2011;16:1535-1546.

Mutlu Kurtbas (iStock)

COLORECTAL CANCER

Colon Cancer Costs, Pathways, and Outcomes

Little information exists as to the adherence by practitioners to cancer practice guidelines and its subsequent effect on costs. Researchers from around the nation evaluated the economics of treating patients with colon cancer based on adherence to a particular cancer practice guideline, and whether adherence to the care pathway resulted in optimal outcomes.

The investigators used a database (MedStat MarketScan) of inpatient and outpatient service use to analyze treatments. The guidelines followed were Level I Pathways, developed by US Oncology. These guidelines are integrated into an electronic health record (EHR) so that clinicians can access them at the point of care.

Two assessments were undertaken. The first was a retrospective cohort analysis of patients identified in the EHR with a diagnosis of primary colon cancer whose first-line chemotherapy or adjuvant treatment began between July 1, 2006, and June 31, 2007, at US Oncology network practices. Cases were classified as adhering to the clinical guidelines (on-pathway) or not (off-pathway).

Clinical Outcomes for Patients Whose Treatment Adhered to or Did Not Adhere to the Clinical Guidelines

Outcome	On-Pathway	Off-Pathway
Disease-Free Survival		
1 yr	91%	72%
2 yr	80%	51%
3 yr	73%	41%
Recurrence/Death End Point	23%	56%
Overall Survival (median, mo)	26.9	20.1[a]

[a]P = .03; hazard ratio, 1.57.

The assessment, also a retrospective cohort design, queried the 4.9 million–record database for cost and health service utilization information. The data analysis focused on patients receiving colon cancer chemotherapy in January to June 2006, who did not receive prior chemotherapy in the previous 12 months. Case information was reviewed manually to determine if the patients' care was on- or off-pathway.

In the first study, of the 910 patients who were eligible under the EHR criteria, 433 (48%) began adjuvant therapy and 477 (52%) had first-line therapy for metastatic disease. On-pathway treatment was conducted in 756 patients (83%) while 154 (17%) received off-pathway treatment. In the 338 patients with stage III disease who began adjuvant therapy, 85 events (recurrence or death) were seen. Recurrence or death were revealed to be less frequent in patients whose treatment complied with the clinical guideline compared with those whose treatment did not (Figure). A total of 229 deaths occurred among the 477 patients who began first-line therapy.

In the second study, of 220 patients who met the study criteria, 41% were treated on-pathway and 59% received off-pathway therapy. Chemotherapy costs, total costs, and the chemotherapy period were significantly lower for adjuvant treatment patients who were on-pathway (n = 80) than off-pathway (n = 70) (P <.05). The mean total cost per case was $103,379 for patients whose treatment adhered to the guidelines versus $156,020 for those whose treatment did not (P <.001). For those receiving metastatic colon cancer chemotherapy, the total costs were $131,059 compared with $191,222, respectively ($P$ = .067).

It seems that better value was validated when patients' treatment of colon cancer adhered to a clinical guideline compared with when their therapy did not follow the guideline. The difference in total costs was highly significant for patients receiving adjuvant chemotherapy. **EBO**

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

The Economics of Cancer Care in the United States

How Much Do We Spend and How Can We Spend It Better?

Expenditures on healthcare in the United States account for approximately 18 percent of gross domestic product.[1] In the absence of cost-controlling changes to the US healthcare system, expenditures are expected to increase even more. It is critically important that all stakeholders, that is, policy makers, payers, providers, and consumers, be represented in the ongoing debate about healthcare reform. A basic understanding of medical economics is necessary for anyone interested in evaluating proposals for reform. During a Medical Economics Clinical Science Forum held December 7 at the 2011 San Antonio Breast Cancer Symposium, Elena Elkin, PhD, Memorial Sloan-Kettering Cancer Center, and Michael Hassett, MD, MPH, Dana-Farber Cancer Institute, attempted to answer 6 basic questions, outlined below, about the cost of cancer care.

ICER – the incremental cost-effectiveness ratio. Represents difference in cost divided by difference in effectiveness between 2 interventions.

$$ICER = \Delta C/\Delta E = (C_2 - C_1 / E_2 - E_1)$$

QALY – Quality-adjusted life-year. Preferred metric for comparative-effectiveness analysis because it: (1) captures impact of disease and treatment on survival and quality of life, both morbidity and mortality, and (2) can be compared across interventions and diseases in dollars per QALY.

U – Utility. Approximates preference for a health state, or the way we feel about or value health-related quality of life. It ranges from 0 (worst imaginable health) to 1 (perfect health). Utility is important when the QALY is used as the metric for cost-effectiveness.

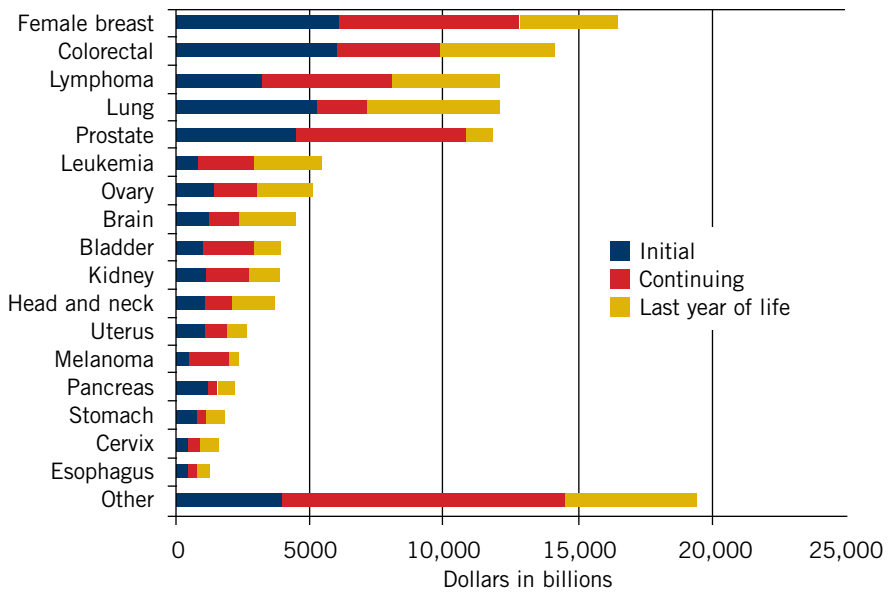
How much do we spend?

Between 1990 and 2009, estimated adjusted annual direct medical spending on cancer in the United States doubled.[2] During 2010, the United States spent an estimated $125 billion on cancer care.[3] Breast cancer spending accounted for 13% ($16.5 billion) of all direct medical spending on cancer in 2010 (Figure 1).[3]

How do we spend it?

Total average Medicare spending per patient for initial phase care of breast cancer (2 months prediagnosis–365 days postdiagnosis) was $21,000 (2002 US$) in 2002 (Figure 2).[4] Surgery and radiation cost little on a per-patient basis: $5700 and $4500 (2002 US$), respectively, and were used in 91% and 51% of patients, respectively. In contrast, chemotherapy and other inpatient services were used in about 25% of patients, but at a higher per-patient cost ($12,800 [2002 US$]). If the data used for this analysis were expanded to include continuing care and end-of-life care, there would be a marked difference in spending patterns. The United States spent an estimated $62,900 to $94,300 per person for end-of-life breast cancer care during 2010 (Figure 1).[3]

Figure 1. Estimated US Expenditures on Cancer Care, by Site and Phase of Care, 2010



US prevalence cost estimates, by phase of care, 2010. An estimated $124.5 billion was spent on cancer care in the United States in 2010, with $16.5 billion spent on breast cancer.

Source: Reprinted with permission from Yabroff KR, Lund J, Kepka D, Mariotto A. Economic burden of cancer in the United States: estimates, projections, and future research. *Cancer Epidemiol Biomarkers Prev.* 2011;20:2006-2014.

How can we spend our money better?

"In order to make good decisions about investments in healthcare, we need information about value. I hope you would all agree with that statement," Dr Elkin remarked. A cost-effectiveness analysis, also known as a cost-utility analysis, is one way to obtain information about value. Cost-effectiveness analyses estimate the value for money of different healthcare interventions through a comparison of incremental costs and incremental health benefits of a new intervention. They can inform decisions about individual healthcare choices, clinical policy, and societal resource allocation with respect to preventive, diagnostic, and therapeutic interventions.

Often, a cost-effectiveness analysis compares a new treatment with an older standard treatment. The end point derived from incremental cost-effectiveness analysis is the incremental cost-effectiveness ratio, or ICER, which can be expressed as cost per quality-adjusted life-year (QALY) (sidebar). Dr Elkin cautioned, "Sometimes in these analyses it is not so black and white. If a new treatment is compared to a very poor, older treatment, it will make the new treatment look better. That is why it is very important in an analysis to understand what they are comparing it to."

The United States does not use cost-effectiveness analysis in making decisions on healthcare expenditures or in setting priorities. As part of their decision-making process, several countries, including the United Kingdom, Canada, and Australia, require formal quantitative evaluation in the form of cost-effectiveness analysis and consider the recommendations of a designated independent agency.[6] Dr Elkin remarked, "I don't think any of us would advocate that cost-effectiveness should be the sole basis for a decision, but I believe that more information can help us make better decisions."

What is good value for money?

Willingness to pay for health gain really defines what is considered a good value for money. Available resources influence it and it varies across people and geographical regions. In the United States, there are no strict criteria for good value in healthcare.

Figure 2. Medicare Spending for Breast Cancer for Initial Phase of Care, 2002

Intervention	Patients Treated (%)[a]	Mean Payment for Each Patient Treated ($)[b,c]	Total Medicare Payment ($)[b,c]	Fraction of Total Payment (%)[d]
Total	100	21,000	1.06 billion	NA
Surgery	91	5700	261 million	25
Radiation	51	4500	117 million	11
Chemotherapy	24	12,800	157 million	15
Other inpatient	23	16,700	194 million	18

[a]Data derived from subgroup (n = 4770) of total study cohort. Subgroup included Medicare beneficiaries 65 years and older diagnosed with breast cancer in 2002 and with claims for specific cancer services.
[b]All payments are in 2002 US$.
[c]Total Medicare payments for initial care were estimated by extrapolating 2002 SEER cancer site–specific rates to US Medicare fee-for-service beneficiaries 65 years and older (n = 50,716).
[d]Not all Medicare payments are included in the reported categories.

Source: Adapted from Warren JL, Yabroff KR, Meekins A, et al. Evaluation of trends in the cost of initial cancer treatment. *J Natl Cancer Inst.* 2008;100:888-897.

Figure 3. Examples of Cost-Effectiveness Analysis in Breast Cancer

Interventions	ICER
BRCA1/2 testing (age 35+, family history of breast or ovarian cancer)	$5400 per QALY
Letrozole vs anastrozole (postmenopausal, HR+)	$26,000 per QALY
Lapatinib vs capecitabine (HER2+ metastatic breast cancer)	$170,000 per QALY
All digital screen mamography vs film mammography, age 40+	$930,000 per QALY

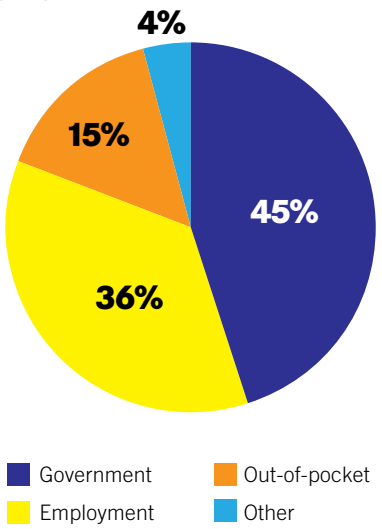
ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
Results of cost-effectiveness analyses for a sample of breast cancer interventions.

Source: Adapted from Elkin EB. The cost of cancer care: how much do we spend and how can we spend it better? 34th Annual CTRC-AACR San Antonio Breast Cancer Symposium; December 2011; San Antonio, TX.

Common perceptions suggest upper limits of good value ranging from $50,000 per QALY to $100,000 per QALY. These thresholds, however, are probably too low, are certainly out of date, and might be contributing to resistance to cost-effectiveness analysis in the United States.[6] As a result, some researchers and stakeholders have discussed updated thresholds for willingness to pay.[6] Adjusting the $50,000 per QALY value (a threshold first proposed in the early 1980s) to 2007 US$ equates to $197,000 per QALY. The World Health Organization's suggested calculation sets the threshold at $140,100 per QALY in 2008 US$. To put things into context, Dr Elkin presented cost-effectiveness estimates for several breast cancer interventions, a sampling of which is shown in Figure 3.[7]

Dr Elkin finished with a few comments about cost-effectiveness versus savings. "Cost-effectiveness is not the same as cost saving. Most medical interventions do not save money; most result in net monetary expenditure….Incremental cost-effectiveness should never be the sole criterion for decision making."

Figure 4. US Healthcare Spending, by Payer



Sources of dollars spent on healthcare in the United States.

Source: Reprinted with permission from Bodenheimer T. High and rising health care costs: part 1: seeking an explanation. *Ann Intern Med*. 2005;142:847-854.

Do we spend too much?

The United States spends more on healthcare than other developed nations.[8] We know from national health expenditure data that annual per person healthcare spending relative to per capita gross domestic product more than doubled between 1990 and 2009; projections through 2019 see a continuation of this trend.[9]

Despite outspending by the United States compared with other developed nations, outcomes in terms of preventable deaths and years of life lost to malignant disease are not better and, in some cases, are significantly worse.[10] Dr Hassett presented the results of an analysis that used Surveillance Epidemiology and End Results (SEER) and Medicare data to look at the relationship between spending in the year after diagnosis, quality of care, and outcomes. In this study, increased expenditures did not correlate with improved quality of care or 5-year overall survival.[11]

Can we control spending?

Government and employment-related coverage pay for the vast majority of US healthcare (Figure 4).[12,13] As a major stakeholder in healthcare spending, the US government has made efforts to control cost; however, the US government does not have a fixed budget or take a unified approach to cost control. The Center for Medicare and Medicaid Services (CMS) sets Medicare payment rates, but there are legal restraints on what measures the agency can take to reduce cost.

The Affordable Care Act and elements of the Stimulus Package were passed by the US government to reduce spending. These pieces of legislation included provisions for:

- Health insurance subsidies
- Health insurance exchanges
- Independent payment advisory board
- "Cadillac plan" tax
- CMS contracts with Accountable Care Organizations
- Incentives for adoption and meaningful use of electronic health records
- Comparative-effectiveness research funding

History has demonstrated that the manner in which government applies its tools can affect not only spending but also utilization. For example, in 2005, changes to Medicare part B reimbursement for chemotherapy effectively reduced payment on many medications. Dr Hassett presented data demonstrating a dramatic drop in paclitaxel usage after the January 2005 payment change, which reduced nominal reimbursement per monthly dosage of paclitaxel by approximately 5-fold.[14] Similarly, approximately 65% of US oncologists reduced their use of erythropoietin-stimulating agents (ESAs) after a national coverage determination by CMS regarding the use of ESAs among oncology patients.[15]

Dr Elkin touched upon this issue during a discussion of value-based insurance, which took place after the presentations. "One of the challenges is let's increase reimbursement for something that is going to be very effective and low cost so that we don't see major dropoffs in utilization of good drugs simply because [reimbursement] has dropped. Doctors [behave rationally], like the rest of us, [and] are going to respond to reimbursement incentives."

Who should decide what we spend and how we spend it?

There are no simple answers to this question and it is really a societal question. Dr Hassett offered perspective by reviewing some of the pros and cons of government, payers, or providers being responsible for decision making. Cost decisions made by society (government) might involve a process that reflects the aggregate priorities of citizens and adopts a single set of standards. In this scenario, however, patients and healthcare providers may end up with less choice. If payers make decisions about cost, a broader array of options regarding the extent of coverage and cost might be available, but critics cite potential inequalities and high administrative costs as drawbacks. Healthcare providers often believe they have a duty to offer a patient any treatment that yields a net benefit regardless of the cost. If they were responsible for considering costs when making treatment decisions, they might be challenged to balance multiple, potentially conflicting responsibilities as taxpayers, business owners, and patient advocates.

During follow-up questioning, Dr Hassett addressed the cost-benefit trade-off of new cancer treatments. "If you look at breast cancer care, there have been significant improvements in outcomes over the last 20 to 30 years. How much better we are going to do relative to how much new treatments are going to cost is a big issue. And, I think it is only going to become more complicated and challenging, in part because our treatments are becoming even more fine tuned." **EBO**

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Technologies Behind Biomarker Discovery and Development

Metabolomics, Proteomics, and Epigenetics

For many years, researchers have recognized the promise that biomarkers hold for advancing the way we think about and treat cancer. Biomarkers are molecules found in biological specimens (eg, blood, bodily fluids, or tissues) that can serve as indicators of normal biological processes, pathogenic processes, or response to medical therapy.[1] Clinical applications of biomarkers in oncology are expected to improve diagnosis, prognosis, prediction of response or recurrence, and disease monitoring. Biomarker discovery and development is moving forward through novel uses of complex technologies.

An educational session at the 2011 San Antonio Breast Cancer Symposium focused on 3 important technologies used in biomarker research: metabolomics, proteomics, and epigenetics. The first speaker was Arun Sreekumar, PhD, Baylor College of Medicine, who talked about metabolomics as a vehicle for biomarker identification and development. Gordon Mills, MD, PhD, University of Texas MD Anderson Cancer Center, followed with a discussion of proteomics. The final speaker, Stephen Baylin, MD, of Johns Hopkins University, provided an overview of epigenetics.

The American Association of Cancer Research, Food and Drug Administration, and National Cancer Institute (AACR-FDA-NCI) Cancer Biomarkers Collaborative defines biomarker discovery and development as a pipeline of linked processes: hypothesis generation, research study design, sample collection, data collection, data analysis, assay development, assay validation, clinical qualification, regulatory approval, and clinical use.[2] Collectively, the speakers touched upon many of these processes. While each speaker concentrated on a particular approach toward biomarker discovery and evaluation, they all adhered to a central theme: the successful application of biomarkers toward the design of combined rational therapy will require integrative efforts that exploit the information provided by these and other technologies.[3,4] Dr Mills summarized the overarching goal of this type of research: "The key goal as we move forward is to have a sufficient understanding of what is happening in our patients' tumors to develop rational combinatorial therapy and link biomarkers of patients who are likely to benefit to the best targeted therapy."

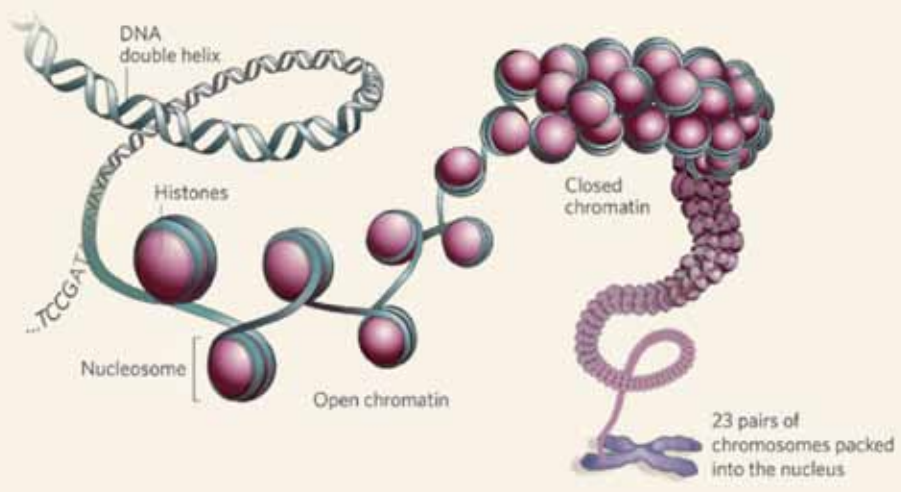
The availability of high-throughput technologies has vastly broadened the potential for untargeted biomarker discovery, making it possible to scan hundreds of molecules at once. All 3 speakers emphasized the importance of establishing validity and maintaining quality control throughout each phase of biomarker discovery and development.

Metabolomics

Metabolomics is the study of metabolites and the metabolome (sidebar). In his talk, Dr Sreekumar defined it as "the comprehensive and simultaneous systematic determination of metabolite levels in the metabolome and their changes over time as a consequence of stimuli, for example, disease, environmental changes, and drugs." He explained that metabolites, as the end products of protein action, serve as cellular physiology indicators.

Dr Sreekumar began his talk by putting genomic, transcriptomic, proteomic, and metabolomic technologies into context with one another. The metabolome comprises about 3000 metabolites, making it less complex than the other "–omic" approaches.[5] According to Dr Sreekumar, they are also more approachable: "Metabolites are much more stable than genes or proteins and can be easily identified in biofluids." Cancer-focused metabolic research is ongoing to identify metabolic markers of disease and tumor-specific biochemical pathways that can serve as druggable targets. During an interview conducted after his presentation, Dr Sreekumar remarked, "There are metabolic tests already available, like in the case of diabetes, you can look at glucose. Testing of metabolites is clinically done for metabolic syndrome, diabetes, and so on, but similar tests in the field of cancer have not come about yet. Our goal is to see whether we can provide such a test."

Figure 1. DNA Organization



DNA is wrapped around proteins called histones to form chromatin, the core unit of which is the nucleosome. When a gene is turned off or repressed, it is usually associated with a nucleosome that is part of a highly ordered structure referred to as closed chromatin. Genes that are turned on, or available for activation, exist in an open chromatin state. Epigenetic modifications can influence whether a gene is turned on or off through their control of the position and density of nucleosome arrangements.

Source: Reprinted with permission from Baylin SB, Schuebel KE. Genomic biology: the epigenomic era opens. *Nature*. 2007;448:548-549.

Proteomics

Proteomics refers to studies of the proteome—the proteins of an organism or cellular system along with any modifications to those proteins—to understand cellular biology. In general, targeted therapies exploit a specific protein product within a perturbed cellular signaling pathway. The benefits of targeted therapies are often short-lived because cells are capable of adaptively responding after exposure to these drugs. These adaptive responses are revealed at the protein level through changes in homeostatic networks, feedbacks, and crosstalks. It is hoped that the identification of the mechanisms behind adaptive responses will inform the design of rational combined therapies. Dr Mills spoke about why it is important to move beyond RNA and DNA studies. "Although we have some incredible targeted therapeutics, as we look at what is going on with patients, most of the time only a subpopulation of patients respond. We obviously do not know why certain subpopulations respond and, in most of the cases, those responses are short-lived."

Protein biomarkers can be assayed using relatively inexpensive standard assays, such as fluorescent in situ hybridization (FISH), enzyme-linked immunosorbent assay (ELISA), and Western blot, already in practice in CLIA-certified laboratories. While protein biomarkers are ripe with potential, their identification has been hampered by the inherent complexities of protein biology and the limitations that current technologies present. Dr Mills reviewed the efforts of the National Cancer Institute's Clinical Proteomic Technolo-

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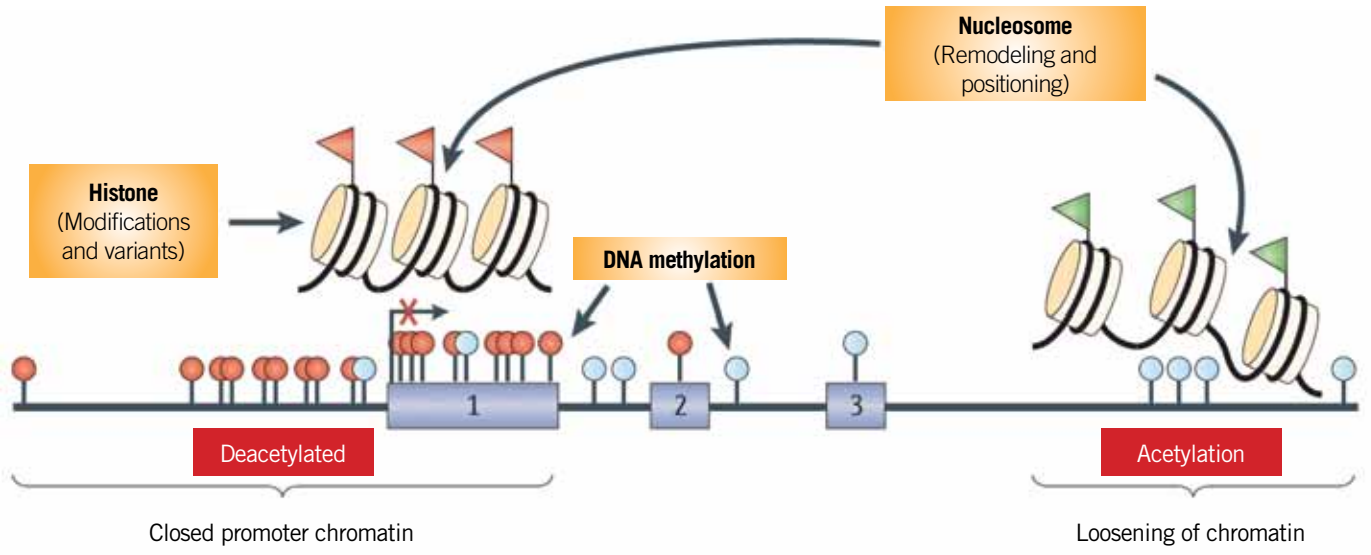
—Gordon Mills, MD, PhD
University of Texas MD
Anderson Cancer Center

Figure 2. A Snapshot of the Cancer Epigenome



The cancer epigenome is characterized by concurrent abnormal gains (red circles) and losses (blue circles) of DNA methylation and histone modifications (red and green flags). Abnormally demethylated and acetylated (green flags) regions of DNA assume an open configuration. In contrast, regions that have been abnormally methylated and deacetylated (red flags) take on a closed conformation, causing gene silencing.

Source: Reprinted with permission from Baylin SB, Jones PA. A decade of exploring the cancer epigenome-biological and translational implications. *Nat Rev Cancer*. 2011;11:726-734.

gies Tumor Analysis Consortium, established to advance proteomics research.[6] It is hoped that information gained from this program's integrative approaches will produce a deeper understanding of cancer biology, with high-quality data sets, reagents, and analytically validated quantitative assays to be made publicly available.

Epigenetics

DNA is subject to a number of modifications that do not involve a change in the actual DNA sequence, for example, methylation of DNA (the addition of a methyl group to a DNA strand) and histone deacetylation (removal of an acetyl group from a histone protein). Epigenetics is the study of functionally relevant changes of this nature (Figure 1).[7]

Dr Baylin focused most of his talk on the deregulation of DNA methylation, just 1 type of epigenetic abnormality (Figure 2).[8] It is becoming apparent that methylation losses and gains happen simultaneously across the cancer genome in a nonrandom manner. In effect, what happens is that some epigenetic changes turn off (repress) critical tumor suppressor genes while other changes maintain genes that drive the cancer in an active configuration.

Next-generation sequencing projects such as the Cancer Genome Atlas Project have revealed that mutations in epigenome-modifying proteins occur at high frequency in cancer cells.[8,9] What these mutations actually mean to the phenotype of the epigenome is not clearly understood. According to Dr Baylin, "This is going to be a big exercise that you are going to see, I predict, over the next few years—linking the change in the hard drive (DNA) to what happens to make the change in packaging of the DNA. I think this is going to be extremely instructive not only in providing targets of therapy all built on this growing understanding but also in our understanding of these genetic and epigenetic linkages."

Earlier in the session, Dr Sreekumar presented published data from a metabolomic analysis of bladder cancer that affirmed the notion that a true understanding of cancer biology is going to come from studies that link all of these fields together. The data demonstrated that deregulation of an important enzyme pathway is linked to epigenetic modifications in the form of methylation.[10]

Therapeutics that target epigenetic aberrations may be able to reverse the changes that shut down tumor suppressors. This differs from the mechanism of many anticancer interventions that aim to kill cancerous cells. In fact, in an ongoing study presented by Dr Baylin, researchers are taking old drugs like the demethylating agent azacitidine and the histone deacetylation inhibitor entinostat and using them at nanogram doses that are much lower than historical cell-killing doses. Early results from a small study involving patients with recurrent non-small-cell lung cancer are promising. Preclinical studies of low dose azacitidine for the treatment of breast cancer are also ongoing, with encouraging preliminary results.

Looking Forward

Cancer treatment decisions are based, for the most part, on cancer type and stage, and not molecular characteristics of the cancer cells. The hope is that biomarkers will enable physicians to base treatment selection on the molecular profile of each patient's cancer.

Most biomarkers identified to date have been stalled in the research setting and have not been carried over to clinical use. Clearing the hurdles that are preventing crossover will require a collaborative effort that brings together scientists and policy makers from a variety of disciplines and who represent academic, private, and public settings.[4]

Dr Mills emphasized this in his introductory statements by saying, "As we move forward to helping patients and translating our observations to patients we have to learn how to work with industry.…Many of the things we are doing are moving forward and we are working with industry in a way that is going to help our patients." **EBO**

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