Bridging the gap between payer and provider perspectives

THE AMERICAN JOURNAL OF MANAGED CARE®

#1 IN CITATIONS & IMPACT FACTOR

Volume 19
Special Issue 3

Evidence-Based Oncology

Payer Trends

Five Trends Emerge in Payer Management of Oncology

Market Dynamics Change How Plans Manage Oral and Office-Administered Agents

Susan Weber

Susan Weber

If there's a "reset" button for oncology drug management, payers are ready to press it. For years, management of these agents has been the exception, not the rule. Although payers have restricted the use of these drugs, they have rarely denied coverage or required heavy cost sharing by patients. But that is poised to change as market dynamics shift and oncology becomes more of a management priority for health plans.

According to research from Health Strategies Group's Managed Care Complete service, oral oncolytics and office-administered oncology agents are now among payers' top 5 management priorities. The reasons for this refocusing

(continued on page SP120)

2012 Cancer Center Business Summit Coverage

Performance Metrics in Oncology

Thomas R. Barr, MBA

In 2011, the Medicare Electronic Health Record (EHR) Incentive Program began paying physicians and hospitals for the measurement and reporting of performance metrics through the utilization of certified electronic medical record software. This epic program began in earnest the irrevocable shift in the provision of healthcare from an individual craft-based art to a structured, evidence-based system. The EHR Incentive program has 3 specific phases that progressively build from data capture and reporting, through clinical process refinement, to the final goal of achieving measurably improved healthcare outcomes.[1] Currently, we are in the first phase of this transition, and in oncology, trends are emerging about what metrics are important to 3 important groups—patients, payers, and providers. Each seeks improvements to quality and lower, or at least stable, costs for cancer care. The broad utilization of electronic medical record technology has, for the first time in history, enabled systematic measures of care delivery on a broad scale.

Thomas R. Barr, MBA

While management of clinical care using modern information technology is important to providers and payers of oncology care, it is

(continued on page SP122)

AJMC.com

Disease Overview

Chemoprevention in Prostate Cancer: Identifying Patients at Greatest Risk May Provide Greatest Value

Marj P. Zimmerman, MS, BS Pharm; and Stanton R. Mehr

Prostate cancer is a common cancer in men that, once it progresses to the later stages, has serious morbidity and mortality consequences as well as burdensome financial issues for patients, the healthcare system, and society. Prostate cancer is a common cancer in men, second only to skin cancer, and is responsible for about 10% of the deaths attributed to all of the cancers.[1] As a result, several strategies have been developed to reduce the morbidity, mortality, and costs associated with prostate cancer. These include the identification of patients at risk, chemoprevention regimens that prevent the development of the disease in those at risk, and the early diagnosis of patients with confirmed disease.

By the Numbers

According to the American Cancer Society, prostate cancer will be diagnosed in about 240,000 men in 2013, and it will be listed as the cause of death in 30,000.[1] African Americans have a higher incidence of prostate cancer than Caucasians and are also more likely to die from the disease. Race, age, and family history are risk factors. Around 2.5 million men currently are prostate cancer patients.[2]

The majority of cases (approximately 60%) are diagnosed in men 65 years and older, and 97% of cases are diagnosed in men at least 50 years of age. The average age at diagnosis is approximately 67 years.[1] Known genetic factors are linked to the disease in about 5% to 10% of patients.[2]

The disease usually has no symptoms and if diagnosed in the early

(continued on page SP127)

Also in this issue...

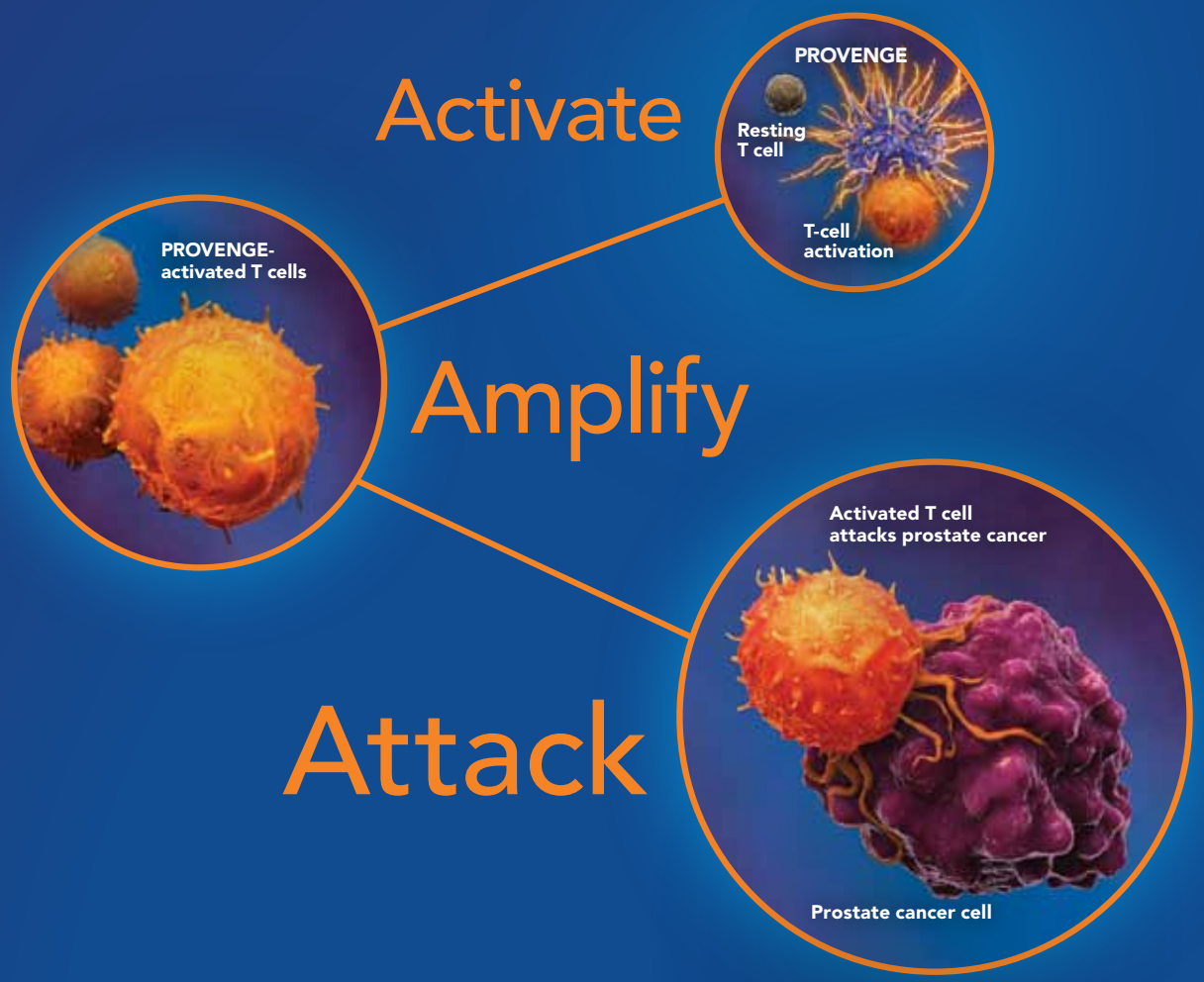
AJMC TV

Darius Lakdawalla, PhD, discusses the payer/provider relationship in oncology management

Dennis Scanlon, PhD, addresses the importance of payer/provider relationships

In advanced prostate cancer

TREAT FIRST LINE WITH PROVENGE TO



EXTEND SURVIVAL

>2 years	Extends median survival beyond 2 years[1]
1st and only	First and only FDA-approved immunotherapy for advanced prostate cancer
1st line	First-line treatment for men with asymptomatic or minimally symptomatic metastatic CRPC *(NCCN Category 1 recommendation)*[2]

INDICATION: PROVENGE® (sipuleucel-T) is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

IMPORTANT SAFETY INFORMATION: PROVENGE is intended solely for autologous use and is not routinely tested for transmissible infectious diseases. In controlled clinical trials, serious adverse events reported in the PROVENGE group included acute infusion reactions (occurring within 1 day of infusion) and cerebrovascular events. Severe (Grade 3) acute infusion reactions were reported in 3.5% of patients in the PROVENGE group. Reactions included chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. No Grade 4 or 5 acute infusion reactions were reported in patients in the PROVENGE group.

The most common adverse events (incidence ≥15%) reported in the PROVENGE group were chills, fatigue, fever, back pain, nausea, joint ache, and headache.

For more information on PROVENGE, please see Brief Summary of Prescribing Information on adjacent page.

www.PROVENGE.com

PROVENGE®
(sipuleucel-T)

PROVENGE® (sipuleucel-T)
Suspension for Intravenous Infusion **Rx Only**

BRIEF SUMMARY – See full Prescribing Information for complete product information

INDICATIONS AND USAGE: PROVENGE® (sipuleucel-T) is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

DOSAGE AND ADMINISTRATION

- **For Autologous Use Only.**
- The recommended course of therapy for PROVENGE is 3 complete doses, given at approximately 2-week intervals.
- Premedicate patients with oral acetaminophen and an antihistamine such as diphenhydramine.
- Before infusion, confirm that the patient's identity matches the patient identifiers on the infusion bag.
- **Do Not Initiate Infusion of Expired Product.**
- Infuse PROVENGE intravenously over a period of approximately 60 minutes. **Do Not Use a Cell Filter.**
- Interrupt or slow infusion as necessary for acute infusion reactions, depending on the severity of the reaction.

(See Dosage and Administration [2] of full Prescribing Information.)

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS

- **PROVENGE is intended solely for autologous use.**
- **Acute infusion reactions** (reported within 1 day of infusion) included, but were not limited to, fever, chills, respiratory events (dyspnea, hypoxia, and bronchospasm), nausea, vomiting, fatigue, hypertension, and tachycardia. In controlled clinical trials, 71.2% of patients in the PROVENGE group developed an acute infusion reaction.

  In controlled clinical trials, severe (Grade 3) acute infusion reactions were reported in 3.5% of patients in the PROVENGE group. Reactions included chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. The incidence of severe events was greater following the second infusion (2.1% vs 0.8% following the first infusion), and decreased to 1.3% following the third infusion. Some (1.2%) patients in the PROVENGE group were hospitalized within 1 day of infusion for management of acute infusion reactions. No Grade 4 or 5 acute infusion reactions were reported in patients in the PROVENGE group.

  Closely monitor patients with cardiac or pulmonary conditions. In the event of an acute infusion reaction, the infusion rate may be decreased, or the infusion stopped, depending on the severity of the reaction. Appropriate medical therapy should be administered as needed.
- **Handling Precautions for Control of Infectious Disease.** PROVENGE is **not** routinely tested for transmissible infectious diseases. Therefore, patient leukapheresis material and PROVENGE may carry the risk of transmitting infectious diseases to health care professionals handling the product. Universal precautions should be followed.
- **Concomitant Chemotherapy or Immunosuppressive Therapy.** Use of either chemotherapy or immunosuppressive agents (such as systemic corticosteroids) given concurrently with the leukapheresis procedure or PROVENGE has not been studied. PROVENGE is designed to stimulate the immune system, and concurrent use of immunosuppressive agents may alter the efficacy and/or safety of PROVENGE. Therefore, patients should be carefully evaluated to determine whether it is medically appropriate to reduce or discontinue immunosuppressive agents prior to treatment with PROVENGE.
- **Product Safety Testing.** PROVENGE is released for infusion based on the microbial and sterility results from several tests: microbial contamination determination by Gram stain, endotoxin content, and in-process sterility with a 2-day incubation to determine absence of microbial growth. The final (7-day incubation) sterility test results are not available at the time of infusion. If the sterility results become positive for microbial contamination after PROVENGE has been approved for infusion, Dendreon will notify the treating physician. Dendreon will attempt to identify the microorganism, perform antibiotic sensitivity testing on recovered microorganisms, and communicate the results to the treating physician. Dendreon may request additional information from the physician in order to determine the source of contamination.

(See Warnings and Precautions [5] of full Prescribing Information.)

ADVERSE REACTIONS

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

The safety evaluation of PROVENGE is based on 601 prostate cancer patients in the PROVENGE group who underwent at least 1 leukapheresis procedure in four randomized, controlled clinical trials. The control was non-activated autologous peripheral blood mononuclear cells.

The most common adverse events, reported in patients in the PROVENGE group at a rate ≥15%, were chills, fatigue, fever, back pain, nausea, joint ache, and headache. Severe (Grade 3) and life-threatening (Grade 4) adverse events were reported in 23.6% and 4.0% of patients in the PROVENGE group compared with 25.1% and 3.3% of patients in the control group. Fatal (Grade 5) adverse events were reported in 3.3% of patients in the PROVENGE group compared with 3.6% of patients in the control group.

Serious adverse events were reported in 24.0% of patients in the PROVENGE group and 25.1% of patients in the control group. Serious adverse events in the PROVENGE group included acute infusion reactions *(see Warnings and Precautions)*, cerebrovascular events, and single case reports of eosinophilia, rhabdomyolysis, myasthenia gravis, myositis, and tumor flare.

PROVENGE was discontinued in 1.5% of patients in Study 1 (PROVENGE group n=341; Control group n=171) due to adverse events. Some patients who required central venous catheters for treatment with PROVENGE developed infections, including sepsis. A small number of these patients discontinued treatment as a result. Monitoring for infectious sequelae in patients with central venous catheters is recommended.

Each dose of PROVENGE requires a standard leukapheresis procedure approximately 3 days prior to the infusion. Adverse events that were reported ≤1 day following a leukapheresis procedure in ≥5% of patients in controlled clinical trials included citrate toxicity (14.2%), oral paresthesia (12.6%), paresthesia (11.4%), and fatigue (8.3%).

Table 1 provides the frequency and severity of adverse events reported in ≥5% of patients in the PROVENGE group of randomized, controlled trials of men with prostate cancer. The population included 485 patients with metastatic castrate resistant prostate cancer and 116 patients with non-metastatic androgen dependent prostate cancer who were scheduled to receive 3 infusions of PROVENGE at approximately 2-week intervals. The population was age 40 to 91 years (median 70 years), and 90.6% of patients were Caucasian.

Table 1 Incidence of Adverse Events Occurring in ≥5% of Patients Randomized to PROVENGE

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Any Adverse Event	**591 (98.3)**	**186 (30.9)**	**291 (96.0)**	**97 (32.0)**
Chills	319 (53.1)	13 (2.2)	33 (10.9)	0 (0.0)
Fatigue	247 (41.1)	6 (1.0)	105 (34.7)	4 (1.3)
Fever	188 (31.3)	6 (1.0)	29 (9.6)	3 (1.0)
Back pain	178 (29.6)	18 (3.0)	87 (28.7)	9 (3.0)
Nausea	129 (21.5)	3 (0.5)	45 (14.9)	0 (0.0)
Joint ache	118 (19.6)	11 (1.8)	62 (20.5)	5 (1.7)
Headache	109 (18.1)	4 (0.7)	20 (6.6)	0 (0.0)
Citrate toxicity	89 (14.8)	0 (0.0)	43 (14.2)	0 (0.0)
Paresthesia	85 (14.1)	1 (0.2)	43 (14.2)	0 (0.0)
Vomiting	80 (13.3)	2 (0.3)	23 (7.6)	0 (0.0)
Anemia	75 (12.5)	11 (1.8)	34 (11.2)	7 (2.3)
Constipation	74 (12.3)	1 (0.2)	40 (13.2)	3 (1.0)
Pain	74 (12.3)	7 (1.2)	20 (6.6)	3 (1.0)
Paresthesia oral	74 (12.3)	0 (0.0)	43 (14.2)	0 (0.0)
Pain in extremity	73 (12.1)	5 (0.8)	40 (13.2)	1 (0.3)
Dizziness	71 (11.8)	2 (0.3)	34 (11.2)	0 (0.0)
Muscle ache	71 (11.8)	3 (0.5)	17 (5.6)	0 (0.0)
Asthenia	65 (10.8)	6 (1.0)	20 (6.6)	2 (0.7)
Diarrhea	60 (10.0)	1 (0.2)	34 (11.2)	3 (1.0)
Influenza-like illness	58 (9.7)	0 (0.0)	11 (3.6)	0 (0.0)
Musculoskeletal pain	54 (9.0)	3 (0.5)	31 (10.2)	3 (1.0)
Dyspnea	52 (8.7)	11 (1.8)	14 (4.6)	3 (1.0)
Edema peripheral	50 (8.3)	1 (0.2)	31 (10.2)	1 (0.3)
Hot flush	49 (8.2)	2 (0.3)	29 (9.6)	1 (0.3)
Hematuria	46 (7.7)	6 (1.0)	18 (5.9)	3 (1.0)
Muscle spasms	46 (7.7)	2 (0.3)	17 (5.6)	0 (0.0)

(Table 1 continued on next page.)

Table 1 Incidence of Adverse Events Occurring in ≥5% of Patients Randomized to PROVENGE

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Hypertension	45 (7.5)	3 (0.5)	14 (4.6)	0 (0.0)
Anorexia	39 (6.5)	1 (0.2)	33 (10.9)	3 (1.0)
Bone pain	38 (6.3)	4 (0.7)	22 (7.3)	3 (1.0)
Upper respiratory tract infection	38 (6.3)	0 (0.0)	18 (5.9)	0 (0.0)
Insomnia	37 (6.2)	0 (0.0)	22 (7.3)	1 (0.3)
Musculoskeletal chest pain	36 (6.0)	2 (0.3)	23 (7.6)	2 (0.7)
Cough	35 (5.8)	0 (0.0)	17 (5.6)	0 (0.0)
Neck pain	34 (5.7)	3 (0.5)	14 (4.6)	2 (0.7)
Weight decreased	34 (5.7)	2 (0.3)	24 (7.9)	1 (0.3)
Urinary tract infection	33 (5.5)	1 (0.2)	18 (5.9)	2 (0.7)
Rash	31 (5.2)	0 (0.0)	10 (3.3)	0 (0.0)
Sweating	30 (5.0)	1 (0.2)	3 (1.0)	0 (0.0)
Tremor	30 (5.0)	0 (0.0)	9 (3.0)	0 (0.0)

*Control was non-activated autologous peripheral blood mononuclear cells.

Cerebrovascular Events. In controlled clinical trials, cerebrovascular events, including hemorrhagic and ischemic strokes, were reported in 3.5% of patients in the PROVENGE group compared with 2.6% of patients in the control group.

(See Adverse Reactions [6] of full Prescribing Information.)

To report SUSPECTED ADVERSE REACTIONS, contact Dendreon Corporation at 1-877-336-3736 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Dendreon Corporation
Seattle, Washington 98101

References: 1. Kantoff PW, Higano CS, Shore ND, et al; for the IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363:411-422.
2. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. V.3.2012. National Comprehensive Cancer Network Web site. www.nccn.org. Accessed April 26, 2012.

Dendreon
Targeting Cancer, Transforming Lives®

PROVENGE®
(sipuleucel-T)

As the healthcare landscape continues to evolve, so too do the efforts to move toward payment systems that place an emphasis on quality of care and cost sharing. But such shifts require an excessive amount of data analysis; pilot studies; and organizations that are willing to think outside of the box to drive healthcare reform components forward.

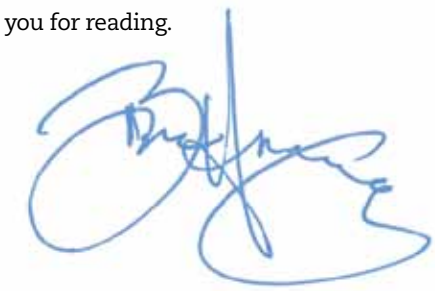
In this issue of the *Evidence-Based Oncology,* Susan Weber of Health Strategies Group in Redwood City, California discusses some of the new trends in the payer management of oncology. In particular, Weber writes about how oral oncolytics and office-administered oncology agents are becoming increasingly important to payers' management priorities, thanks in large part to new market factors and payer capabilities. One potential outcome for this shift will be the evolution of new benefit designs to allow for high cost-sharing requirements as they apply to newly approved oral oncolytics. "Half of [existing] plans already require members to pay additional fees for office-administered drugs, and more plans will follow suit," writes Weber.

"Pullquote info here."

Also in this issue, Stanton R. Mehr provides an outlook of value-based contracting, a strategy that has been gaining momentum in the oncology space. "Comparative-effectiveness research and results reporting has compelled health plans and insurers to sharpen their focus on incorporating this information into coverage decision making," says Mehr. But as is often the case in healthcare, payer adoption of new strategies will vary. Many health plans are currently more concerned with efforts to improve patient and physician support, rather than incorporating penalties and coverage denials.

While our healthcare system in general is undergoing extensive changes, the oncology field in particular is poised to undergo a complete transformation in terms of how care is both delivered and reimbursed. The goal for Evidence-Based Oncology is to ensure that the latest strategies and data are delivered to you by professionals who are experiencing and studying these changed firsthand. Such large decisions and shifts in strategy cannot be achieved without being well informed on the latest pilot studies and innovations. We look forward to serving you as the evolution continues. Thank you for reading.

Thank you for reading.



Brian Haug
Publisher

EDITORIAL MISSION

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

In This Issue...

THE AMERICAN JOURNAL OF MANAGED CARE

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

Bundled Payment: Practice Savior or Killer?

Kurt Ullman

The new "in" term among those looking to lower the cost of health care is "bundled payment" (BP). Although there is still disagreement about what it means, the bundling of payments revolves around oncologists being paid a set fee for managing their patients' care.

"Five or 10 years ago, the oncology spend was not high on the payer's priority list," said Matthew Farber, MA, director of provider economics and public policy, at the Association of Community Cancer Centers in Rockville, Maryland. "As the number of patients goes up, the number of those who survive increases and the general demographic shifts, the cost of cancer care goes up. In addition, the recent run of new (and expensive) drug approvals has caused payer's focus to turn toward oncology."

Matthew Farber, MA

Concerns about BP in cancer treatment

True bundled payments would give the oncologists a single amount of money per patient to cover all costs from initial visit through to discharge from care or to hospice. There are concerns that a BP system would not work in cancer treatment, and could cause disruptions in practices.

One reason is that cancers are a very individualized and diverse group of diseases. To say that a payer will offer a set amount of money for 2 lines of treatment will have to address who is responsible should a third be needed. There is enough variability in oncology that true BP is likely to be problematic.

"Oncologists do not take care of large populations of patients where you can mitigate the risk of outliers who utilize a lot of costs, time, and energy," noted Bruce Gould, MD, medical director of Northwest Georgia Oncology Centers in Marietta, Georgia. "Any payment system has to reflect this so that one or two expensive patients don't break a practice."

Episode of care a better fit?

The model that may be the best payment fit for oncologists is episode of care (EOC). As currently evolving, this transfers a specific part of the risk to the oncologists, but one that is easier to manage.

Gould's group is participating in an early pilot in cooperation with United Healthcare. The participants defined 19 categories for lung, breast, and colon cancers.

"They have taken our margins for chemotherapy medications, added extra money for hospitalizations, and that is what we get when a patient is registered as an EOC fee," said Gould. "We are still paid a fee-for-service when we see the patients in our offices and to administer the medications. The drugs are reimbursed at Average Sales Price."

The insurance company knows what its medicine costs will be and the most it has to spend for physician services should its enrollees need hospital treatment. It hopes to save money by giving oncologists incentives to treat patients in the office (where they get paid) and not in the hospital. Hospital in-patient costs are still paid by the insurance company. The oncologists are only assuming the risk for their in-hospital services.

Shifts in how practices make money

How practices make their money is shifting, and getting the bulk of income from drug charges is past. Other responses by oncologists such as pay for administering medications and increasing in-office diagnostic radiology have come under greater scrutiny.

"This gradual reduction in payment is a long-term trend that practices have to recognize to stay afloat," said Farber. "I think eventually fee-for-service for both Medicare and private insurers is going down. Instead they will pay for better, more efficient, and less duplicative care."

Because of this, it is important for practices to take a long and close look at their processes and find ways to streamline them. Physicians, according to both experts, should look to implementing established clinical guidelines as a first step. But they will also need to update information-gathering abilities through use of electronic medical record (EMR) programs tracking both what they are doing well and where they need to improve.

What practices should consider

Compare current treatment modalities with guidelines from the National Comprehensive Cancer Network (NCCN) or other professional sources. Getting a physician to buy in is important, as just 1 opting out of the predetermined treatment regimens could harm the program for all. This also highlights the need for ways to monitor compliance.

Full commitment to EMR technology is another important part of this puzzle. Both BP and EOC require practices to have the ability to monitor, document, and report treatment regimens. These systems help analyze costs, an important part of the process when negotiating your fee and managing your costs.

Practice business management may play as big a role in profitability as the medical management side. For example, the efficiency and accuracy of your coding and billing staff will impact on your cash flow.

"The investment in a strong management team is not cheap, but will pay dividends and keep practices strong and independent," said Gould. "Over the last few years all of the fat has been removed from the system. If you don't have a lean, mean practice that is collecting every penny due you on the first try, the chances the practice will fold increase."

Bruce J. Gould, MD

How long to get ready?

There is some disagreement on how long practices have to get themselves ready for whichever system wins out. Gould thinks the "ability to worry about

pull

tomorrow is gone," with an immediate need to get the office in order.

On the other hand, Mr Farber thinks there is still time for practices to watch the early adopters work out the kinks. Both agree that keeping track of the various models as they mature is important so that you are "leaning" the right way when approached. They also concur that things like establishing EMRs and familiarizing physicians with guidelines should begin immediately. **EBO**

Author Affiliation: From KVU Communication, Inc, Carmel, IN.

Funding Source: None.

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

Authorship Information: Drafting of the manuscript; critical revision of the manuscript for important intellectual content; and administrative, technical, or logistic support; and supervision.

NEW INDICATION: ZYTIGA® (abiraterone acetate) is indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC).

NOW APPROVED

FOR PATIENTS WITH mCRPC WHO HAVE PROGRESSED ON ADT

ADT = androgen-deprivation therapy.

IMPORTANT SAFETY INFORMATION

- **Contraindications**—ZYTIGA® is not indicated for use in women. ZYTIGA® can cause fetal harm (Pregnancy Category X) when administered to a pregnant woman 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 blood pressure, hypokalemia, or 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 (in study 1) or NYHA Class II to IV heart failure (in study 2) because these patients were excluded from these randomized clinical trials. 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 was reported 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**—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.
- **Increased ZYTIGA® Exposures With Food**—ZYTIGA® must be taken on an empty stomach. 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.

INTRODUCING

AN EXPANDED BODY OF EVIDENCE

More than 20,000 patients with mCRPC have received ZYTIGA® (post-chemotherapy with docetaxel) to date.†[1]

MECHANISM OF ACTION

ZYTIGA® is a CYP17 (17α-hydroxylase/C17, 20-lyase) inhibitor that inhibits androgen production at 3 sources: the testes, adrenal glands, and the prostate tumor tissue itself.

NEW EFFICACY DATA—In a recent Phase 3 clinical trial in patients with mCRPC who had progressed on ADT and had not received chemotherapy.*

Efficacy was also demonstrated in a Phase 3 trial of patients who had received prior chemotherapy containing docetaxel.*

once-daily

Zytiga®
(abiraterone acetate)
250 mg tablets

ZytigaOne™ is your single source for personalized access services for you and your patients: Visit www.zytigaone.com or call 1-855-998-4421.

ZytigaOne™ SUPPORT
The Janssen Biotech Support System

- **Adverse Reactions**—The most common adverse reactions (≥ 10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection, and contusion.

  The most common laboratory abnormalities (> 20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT, and hypokalemia.
- **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. *In vitro*, ZYTIGA® inhibits CYP2C8. There are no clinical data on its use with drugs that are substrates of CYP2C8. Patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate.

  Based on *in vitro* data, ZYTIGA® is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors or inducers on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution during treatment with ZYTIGA®.
- **Use in Specific Populations**—Do not use ZYTIGA® in patients with baseline severe hepatic impairment (Child-Pugh Class C).

***Study Designs:** ZYTIGA®, in combination with prednisone, was evaluated in 2 Phase 3, randomized, double-blind, placebo-controlled, multicenter trials in patients with mCRPC. Study 1 enrolled patients who received prior chemotherapy containing docetaxel (N = 1,195), whereas Study 2 enrolled patients who had not received prior chemotherapy (N = 1,088). In both studies, patients were using a luteinizing hormone-releasing hormone agonist or were previously treated with orchiectomy. In the active treatment arms, patients received ZYTIGA® 1,000 mg orally once daily + prednisone 5 mg orally twice daily. In the control arms, patients received placebo orally once daily + prednisone 5 mg orally twice daily. In Study 1, the primary efficacy endpoint was overall survival. In Study 2, the coprimary efficacy endpoints were overall survival and radiographic progression-free survival.*

† *Estimate based on sales and use data from May 2011 to November 2012.*

Reference: 1. Data on file. Janssen Biotech, Inc.

www.zytigahcp.com

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

K08Z121176

Janssen Biotech, Inc.

12/12 08Z12264B

Janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

ZYTIGA® (abiraterone acetate) Tablets
Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

CONTRAINDICATIONS

Pregnancy: ZYTIGA can cause fetal harm when administered to a pregnant woman. ZYTIGA is not indicated for use in women. 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, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss *[see Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess: ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition *[see Clinical Pharmacology (12.1) in full Prescribing Information]*. In the two randomized clinical trials, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with ZYTIGA *[see Adverse Reactions]*.

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. Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with left ventricular ejection fraction < 50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established because these patients were excluded from these randomized clinical trials *[see Clinical Studies (14) in full Prescribing Information]*. 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: Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking ZYTIGA and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported 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: In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking ZYTIGA. No deaths clearly related to ZYTIGA were reported due to hepatotoxicity events.

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.

Increased ZYTIGA Exposures with Food: 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]*.
- Increased ZYTIGA Exposures with Food *[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.

Two randomized placebo-controlled, multicenter clinical trials enrolled patients who had metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy. In both Study 1 and Study 2 ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to control patients.

The most common adverse drug reactions (≥10%) reported in the two randomized clinical trials that occurred more commonly (>2%) in the abiraterone acetate arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (>20%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the abiraterone acetate arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

Study 1: Metastatic CRPC Following Chemotherapy: Study 1 enrolled 1195 patients with metastatic CRPC who had received prior docetaxel chemotherapy. Patients were not eligible if AST and/or ALT ≥ 2.5X ULN in the absence of liver metastases. Patients with liver metastases were excluded if AST and/or ALT > 5X ULN.

Table 1 shows adverse reactions on the ZYTIGA arm in Study 1 that occurred with a ≥2% absolute increase in frequency compared to placebo or were events of special interest. The median duration of treatment with ZYTIGA was 8 months.

Table 1: Adverse Reactions due to ZYTIGA in Study 1

System/Organ Class Adverse reaction	ZYTIGA with Prednisone (N=791) All Grades[1] % Grade 3-4 %	Placebo with Prednisone (N=394) 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
Injury, poisoning and procedural complications		
Fractures[5]	5.9 / 1.4	2.3 / 0
Cardiac disorders		
Arrhythmia[6]	7.2 / 1.1	4.6 / 1.0
Chest pain or chest discomfort[7]	3.8 / 0.5	2.8 / 0
Cardiac failure[8]	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 all fractures with the exception of pathological fracture
[6]Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[7]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).
[8]Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Table 2 shows laboratory abnormalities of interest from Study 1. Grade 3-4 low serum phosphorus (7%) and low potassium (5%) occurred at a greater than or equal to 5% rate in the ZYTIGA arm.

Table 2: Laboratory Abnormalities of Interest in Study 1

Laboratory Abnormality	Abiraterone (N=791) All Grades (%) Grade 3-4 (%)	Placebo (N=394) All Grades (%) Grade 3-4 (%)
Hypertriglyceridemia	62.5 / 0.4	53.0 / 0
High AST	30.6 / 2.1	36.3 / 1.5
Hypokalemia	28.3 / 5.3	19.8 / 1.0
Hypophosphatemia	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

Study 2: Metastatic CRPC Prior to Chemotherapy

Study 2 enrolled 1088 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT ≥ 2.5X ULN and patients were excluded if they had liver metastases.

Table 3 shows adverse reactions on the ZYTIGA arm in Study 2 that occurred with a ≥ 2% absolute increase in frequency compared to placebo. The median duration of treatment with ZYTIGA was 13.8 months.

Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2

System/Organ Class Adverse reaction	ZYTIGA with Prednisone (N=542) All Grades[1] % Grade 3-4 %	Placebo with Prednisone (N=540) All Grades % Grade 3-4 %
General disorders		
Fatigue	39.1 / 2.2	34.3 / 1.7
Edema[2]	25.1 / 0.4	20.7 / 1.1
Pyrexia	8.7 / 0.6	5.9 / 0.2
Musculoskeletal and connective tissue disorders		
Joint swelling/ discomfort[3]	30.3 / 2.0	25.2 / 2.0
Groin pain	6.6 / 0.4	4.1 / 0.7
Gastrointestinal disorders		
Constipation	23.1 / 0.4	19.1 / 0.6
Diarrhea	21.6 / 0.9	17.8 / 0.9
Dyspepsia	11.1 / 0.0	5.0 / 0.2
Vascular disorders		
Hot flush	22.3 / 0.2	18.1 / 0.0
Hypertension	21.6 / 3.9	13.1 / 3.0
Respiratory, thoracic and mediastinal disorders		
Cough	17.3 / 0.0	13.5 / 0.2
Dyspnea	11.8 / 2.4	9.6 / 0.9
Psychiatric disorders		
Insomnia	13.5 / 0.2	11.3 / 0.0
Injury, poisoning and procedural complications		
Contusion	13.3 / 0.0	9.1 / 0.0
Falls	5.9 / 0.0	3.3 / 0.0
Infections and infestations		
Upper respiratory tract infection	12.7 / 0.0	8.0 / 0.0
Nasopharyngitis	10.7 / 0.0	8.1 / 0.0
Renal and urinary disorders		
Hematuria	10.3 / 1.3	5.6 / 0.6
Skin and subcutaneous tissue disorders		
Rash	8.1 / 0.0	3.7 / 0.0

[1]Adverse events graded according to CTCAE version 3.0
[2]Includes terms Edema peripheral, Pitting edema, and Generalized edema
[3]Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

Table 4 shows laboratory abnormalities that occurred in greater than 15% of patients, and more frequently (>5%) in the ZYTIGA arm compared to placebo in Study 2. Grade 3-4 lymphopenia (9%), hyperglycemia (7%) and high alanine aminotransferase (6%) occurred at a greater than 5% rate in the ZYTIGA arm.

Table 4: Laboratory Abnormalities in > 15% of Patients in the ZYTIGA Arm of Study 2

Laboratory Abnormality	Abiraterone (N = 542)		Placebo (N = 540)	
	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
Hematology				
Lymphopenia	38.2	8.7	31.7	7.4
Chemistry				
Hyperglycemia[1]	56.6	6.5	50.9	5.2
High ALT	41.9	6.1	29.1	0.7
High AST	37.3	3.1	28.7	1.1
Hypernatremia	32.8	0.4	25.0	0.2
Hypokalemia	17.2	2.8	10.2	1.7

[1]Based on non-fasting blood draws

Cardiovascular Adverse Reactions: In the combined data for studies 1 and 2, cardiac failure occurred more commonly in patients treated with ZYTIGA compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients taking ZYTIGA and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

In Study 1 and 2, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arms and no deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiorespiratory arrest in the ZYTIGA arms and 3 (0.3%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the ZYTIGA arms.

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]*.

In vitro, ZYTIGA inhibits CYP2C8. There are no clinical data on the use of ZYTIGA with drugs that are substrates of CYP2C8. However, patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate.

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 can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no adequate and well-controlled studies with ZYTIGA in pregnant women and ZYTIGA is not indicated for use in women, it is important to know that maternal use of a CYP17 inhibitor could affect development of the fetus. Abiraterone acetate caused developmental toxicity in pregnant rats at exposures that were lower than in patients receiving the recommended dose. 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, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with ZYTIGA.

In an embryo-fetal developmental toxicity study in rats, abiraterone acetate caused developmental toxicity when administered at oral doses of 10, 30 or 100 mg/kg/day throughout the period of organogenesis (gestational days 6-17). Findings included embryo-fetal lethality (increased post implantation loss and resorptions and decreased number of live fetuses), fetal developmental delay (skeletal effects) and urogenital effects (bilateral ureter dilation) at doses ≥10 mg/kg/day, decreased fetal ano-genital distance at ≥30 mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses ≥10 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients.

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

Geriatric Use: Of the total number of patients receiving ZYTIGA in phase 3 trials, 73% of patients were 65 years and over and 30% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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.

ZYTIGA® (abiraterone acetate) Tablets

Storage and Handling: Store at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted in the range from 15ºC to 30ºC (59ºF 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]*.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- Patients should be informed that ZYTIGA and prednisone are used together and that they should not interrupt or stop either of these medications without consulting their physician.
- Patients receiving GnRH agonists should be informed that they need to maintain this treatment during the course of treatment with ZYTIGA and prednisone.
- Patients should be informed that ZYTIGA must not be taken with food and that 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. They should be informed that the tablets should be swallowed whole with water without crushing or chewing. Patients should be informed that taking ZYTIGA with food causes increased exposure and this may result in adverse reactions.
- Patients should be informed that ZYTIGA is taken once daily and prednisone is taken twice daily according to their physician's instructions.
- Patients should be informed that in the event of a missed daily dose of ZYTIGA or prednisone, they should take their normal dose the following day. If more than one daily dose is skipped, patients should be told to inform their physician.
- Patients should be apprised of the common side effects associated with ZYTIGA, including peripheral edema, hypokalemia, hypertension, elevated liver function tests, and urinary tract infection. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Patients should be advised that their liver function will be monitored using blood tests.
- Patients should be informed that ZYTIGA may harm a developing fetus; thus, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves. Patients should also be informed that it is not known whether abiraterone or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The patient should use a condom and another effective method of birth control if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with ZYTIGA.

Manufactured by:
Patheon Inc.
Mississauga, Canada

Manufactured for:
Janssen Biotech, Inc.
Horsham, PA 19044

Revised: December 2012

2000005445

K08Z121174A

janssen

Applying Accountable Care to Oncology: Developing an Oncology ACO

Stanton R. Mehr

Ira Klein, MD

The accountable care organization (ACO) has been the buzzword on the tip of everyone's tongue. With January's announcement by the Centers for Medicare & Medicaid Services of an additional 106 ACOs, the number joining the Medicare Shared Savings Program is now 259, serving 4 million beneficiaries.[1] An estimate by the consultant organization Leavitt Partners pegs the number of active ACOs at 428, operating in 49 states.[1]

The principal ideas underlying the ACO concept are (1) coordination of care through integrated services (or virtually integrated services) and (2) financial incentives for clinicians and hospitals to efficiently manage patients, saving money in the process, and in the Accountable Care Act's Medicare Shared Savings initiative,[2] sharing those savings with the provider-partners in the ACO. The majority of ACOs have focused on primary care. Policy makers agree that the ACO concept is most easily applied to primary care, which may have the highest payoff in terms of cost savings through disease prevention and early diagnosis and management.

A few specialty models of ACOs are being piloted, but these are more dependent on secondary prevention of disease episodes or complications. For example, DaVita (www.davita.com), based in Denver, focuses on patients with kidney disease and owns more than 1900 outpatient dialysis centers.[3] Its Accountable Kidney Care Collaborative seeks to use the ACO model for patients with end-stage renal disease. The cost-saving potential of specialty or disease-specific ACOs can be huge, because of the existing costs associated with treating these patients, but it is unclear whether these specialty services are more efficiently provided through their own ACO or as ancillary to the burgeoning primary care ACO marketplace.

Considerations in an Oncology ACO Model

The various common cancer types and multitude of therapies used to treat them may complicate the mission of an ACO. For patients with advanced kidney dysfunction, a specialty ACO may expect savings to be derived from lower hospitalization costs through improved patient care. Considering the cost of treating many neoplasms, should cost savings be a primary goal? Perhaps the principal mission of an oncology ACO would be to better standardize care pathways, use integrated care, and improve counseling of patients in how to manage the course of disease.[3]

If this is the case, oncology ACOs focused on the shared-savings model will likely come up short. In fact, the choice of whether to treat actively or simply monitor a cancer's progress (ie, watchful waiting in prostate cancer) may be money saving to the ACO, but may seem to others as a sign that the organization is willfully withholding care in order to save money.[3] This challenge ensures that the decision making and clinical pathways must be dictated by the clinicians, not the organization.

Of course, the question of developing an oncology-based ACO should not imply that present ACOs do not provide oncology services through their networks. A survey conducted in 2011 found that health plans and health systems forming ACOs were indeed including oncology providers in their plans.[4] According to health plan and health system executives who were forming ACOs, 65% indicated that oncology services were closely aligned or already employed by the organization (**Figure 1**). Another 30% had loose affiliations with oncology providers. Overall, the executives responding to the survey questioned whether a cancer-related ACO model would be the way forward. They indicated that because of the complex issues associated with oncology care (and other specialty-treated diseases, for that matter), most were more focused on learning how the ACO will perform in clinical areas that have more predictable costs, like primary care.

AJMC.com

Scan for additional content.

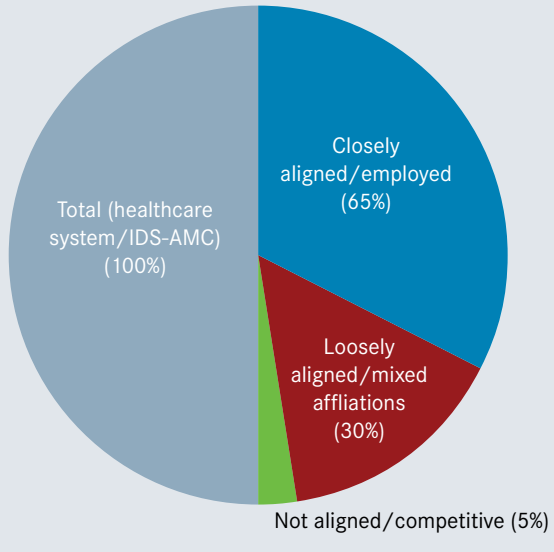
Ira Klein, MD, discusses quality measures in oncology (http://goo.gl/RQ5Rp)

Two Health Plans Take the Lead

Despite these challenges, Florida Blue (Blue Cross and Blue Shield of Florida) recently dove headlong into the oncology ACO arena. First, in May 2012, the insurer announced an agreement with Baptist Health South Florida and Advanced Medical Specialties, which provides oncology services in Miami, to form an oncology ACO. Next, in December 2012, Florida Blue unveiled an oncology ACO with Moffitt Cancer Center in Tampa.[5] This collaboration will focus on common cancers and will "identify and select quality metrics for the program." Slated to start this year, Florida Blue and Moffitt hope to improve patient care by sharing clinical and administrative claims data. It seems that this venture will seek to incorporate a value-based reimbursement system. Additionally, this agreement will emphasize patient engagement in their care and provide services for family members who care for the patients, in an effort to reduce costs overall and improve outcomes.[3] In the press release announcing the agreement, Dr Alan F. List, president and CEO of Moffitt, said, "This partnership with Florida Blue focuses on the value we provide our patients, and that becomes a positive for everyone. I anticipate that we will learn a lot from this new venture and that it will help us to continue to improve cancer care."

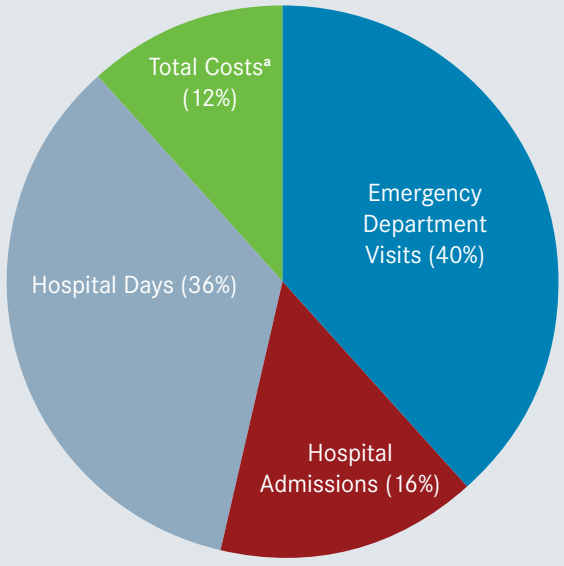
Aetna has been involved with oncology ACO model formation for the past few years. The health plan doesn't view it simply as a new way to pay physicians. Aetna views it as necessary to try to move clinical pathways front and center in the oncologists' offices. Ira Klein, MD, chief of staff to Aetna's chief medical officer, and the head of its oncology strategy, told *Evidence-Based Oncology*, "Cancer care is among the top 3 highest medical cost categories in the

Figure 1. Oncology Positioning Within ACO Responder Organizations: 2011



ACO indicates accountable care organization; IDS-AMC,
Source: Adapted from Barkley R. Where does oncology fit in the scheme of accountable care? *J Oncol Pract.* 2012;8:71-74.

Figure 2. Greater Efficiency: Preliminary Results of Aetna's Oncology ACO Compared With Those Not in the ACO



ACO indicates accountable care organization.
[a]Lung, breast, and colon cancers only.

United States. Oncology also is an area of clinical care that is characterized by high variability in costs and treatment choices across the country. Given this large medical cost footprint and significant potential for clinical improvement, we believed and showed that applying evidence-based guidelines—pathways—to cancer care can help address the variability and get to equal or better health outcomes and lower costs."

He noted that widespread adoption of a pathways-based model requires changes in the approach to care, decision support, and payment. "Supporting oncologists through these changes is critical," said Dr Klein, "and new contractual relationships must drive positive change for their practices and their patients."

Aetna teamed with US Oncology Network's Texas Affiliate, announcing the results of a shared savings model at the American Society of Clinical Oncology symposium in late 2012.[6] According to Aetna, members in the program had at least the same clinical outcomes as members not under the shared savings program, but emergency department and hospital visits dropped significantly, as did hospital admissions and hospital days (**Figure 2**). This resulted in 12% lower costs overall for lung, breast, and colorectal cancers alone.

"The concept for a shared savings model came from the understanding that oncology care is clinically complex in almost every case," commented Dr Klein. "A comprehensive oncology management strategy starts with patients and the goal of adding value to their cancer therapies. But unless incentives are aligned, there's no traction for the physicians and support staff to undertake the difficult work of practice change at the office level. We feel that to gain increased value, you have to flip the coin to the other side and negotiate shared risk.

"We replaced the traditional buy-and-bill model with a system that is rewarding in more appropriate ways, including payment redesign and use of a medical home model approach to patient care. We offer greater payment as an incentive for adherence to pathways, especially with regard to prescribing generic drug products when appropriate. The payment structure also focuses on what physicians do for patients in the office as well as what they do to keep them out of the need for care."

What, if any, early lessons have plans learned about developing the relationships necessary for an oncology ACO? According to Dr Klein at Aetna, "Physicians are a key component to the success of pathways implementation, and aligned incentives are a must. Having a trusted relationship with oncologists is critical as well, because they are providing the care. Without their input, no program can really be effective."

He also pointed out that "Physicians also have an important role in helping the insurer gather and analyze data, which can help in developing additional program goals going forward. We require some mechanism of data capture and strongly encourage interactive electronic clinical decision support tools. This gives us an unbiased activity reporting, which we can then use to feed the 'plan, do, check, act' cycle of quality improvement back to the physicians and offices at the practice level."

Dr Klein noted that from earlier pilots, they realized that oncologists appreciated these tools as learning guides. "Process improvement reduces error while teaching about habits, both good and bad."

And what of Aetna's long-term goals? "While we focus on tools used within practices for many reasons (workflow, precertification relief, error reduction), we will be looking to connect the in-office environment with the care delivery ecosystem outside the oncology office in the future," replied Dr Klein. "Oncologists can be ideal 'medical neighbors' in medical home–type integrated delivery systems. In an ACO, it's all about working together. This can be parlayed into bundles of care, as well."

Additional pilot programs in oncology ACOs are being sponsored by Blue plans in California, Maryland, Michigan, New Jersey, Tennessee, and South Carolina.[4]

Tackling Oncology Care Payments

One of the daunting challenges when considering shared savings methods for oncologists, as well as many other specialties, is the use of fee-for-service reimbursement, along with the "buy-and-bill" system for purchasing oncology medications, both sources of revenue for the oncology practice. Medicare and commercial plans have moved to average manufacturer price–based billing for drugs, which have limited buy-and-bill practices in recent years, but these issues need to be tackled before oncology ACOs can be developed in the mainstream.

UnitedHealthcare, though not starting an oncology ACO per se, has a pilot program (more of a patient-centered medical home model) which may help set benchmarks as to how oncology providers can be paid in such an organization. In this pilot, providers are paid on an episode-of-care basis. This pilot involves 5 oncology practice sites.[7] The episodes of care were defined by the practices themselves for 19 cancer subcategories. This payment for cancer care is fixed, and drugs are reimbursed only at the manufacturer's cost, discouraging buy-and-bill practices. Patient visits are billed separately, and UnitedHealthcare also pays oncology practices a case management fee, which may promote better coordination of care.[7]

In this move away from fee-for-service payments, which would be unworkable in an ACO or shared savings environment, the up-front episode-of-care fee covers the usual treatment period for a patient with breast, lung, or colon cancer. If the cancer recurs, this episode-of-care payment can be renewed every 4 months during the course of the disease. This provides the continuity of payment needed for oncologists to continue overseeing the patient's care (regardless of whether drug therapy is utilized).

This move is echoed by the efforts of others, such as those by Andrew Pecora, MD, president of the New Jersey–based Regional Cancer Care Associates, which was featured in the last issue of *Evidence-Based Oncology*.[8] From the standpoint of building ACOs, it looks like a move in the right direction. **EBO**

Funding Source: None.
Author Disclosure: Mr Mehr reports receiving payment for involvement in the preparation of this article.
Authorship Information: Concept and design; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

References

1. Accountable care organizations have more than doubled since 2011 (press release). Leavitt Partners, February 20, 2013. http://news.leavittpartners.com/newsrelease-cid-1-id-48.html. Accessed February 22, 2013.
2. Medicare Program; Medicare Shared Savings Program: Accountable Care Organizations. CMS-1345-P. *Federal Register,* Vol. 76, Issue 67. November 2, 2011.
3. Stagg Elliott V. Disease-specific ACOs make their debut. American Medical News, January 28, 2013. www.ama-assn.org/amednews/2013/01/28/bisb0128.htm. Accessed January 31, 2013.
4. Barkley R. Where does oncology fit in the scheme of accountable care? *J Oncol Pract*. 2012;8:71-74.
5. Florida Blue and Moffitt Cancer Center Create Cancer-Specific Accountable Care Arrangement (press release). Florida Blue, December 20, 2012. www3.bcbsfl.com/wps/portal/bcbsfl/newsroom?WCM_GLOBAL_CONTEXT=. Accessed January 31, 2013.
6. Aetna, the US Oncology Network provide more evidence that clinically proven, integrated cancer care enhances quality and controls costs: positive outcomes from new study presented at ASCO Quality Care Symposium. Aetna, December 6, 2012. http://newshub.aetna.com/press-release/products-and-services/aetna-us-oncology-network-provide-more-evidence-clinically-prove. Accessed January 12, 2013.
7. Blum K. Episodic payment put to the test. Clinical Oncology News, December 2010. www.clinicaloncology.com/ViewArticle.aspx?d=Policy+and+Management&d_id=151&i=December+2010&i_id=685&a_id=16263. Accessed January 15, 2013.
8. Focusing on clinical and economic outcomes—not guidelines: is it time for a new direction in oncology care? *Am J Manag Care.* 2013(1 Spec No.):SP43.

THE AMERICAN JOURNAL OF MANAGED CARE

Measuring Quality Cancer Care

Robert Gamble

Two of my favorite activities are running and salt-water fishing. Both are very precise and numbers-oriented activities. Running is about time, pace, distance, calorie burn rates, and heart rate zones, among other factors. When talking with runners it does not take long for the conversation to come around to the essential questions: "What is your PR (personal record) for a half (or full) marathon?" or "What is your average weekly miles?" Both of these questions reflect standard benchmarks of the level of accomplishment in the sport.

Fishing, or as we say in the South, "fishin'," has its own set of standards. Before we graduate to the point of hoping the fish do not bother us, we are watchful of length, weight, creel limit, and also making sure the catch falls within season. Measurement is serious business, to the point that the fishing industry has its own "Golden Rule"—an official calibrated tool to measure the length of a fish. Woe to the person who is caught with a fish under or over the size requirements. The fisherman strives to have the best answer to the routine question, "Did you catch anything?" If that is answered in the affirmative the next question will hopefully be answered with a boast: "Any size?"

Both of these activities have finite and very specific criteria of what is considered "good" or "excellent." Why is it we struggle with the similar concepts in healthcare and particularly cancer care? It is interesting that healthcare accounted for 15.2% of GDP in 2008.[1] Fishing (even when included in the category of agriculture, hunting, forestry, and fishing) is only 1.1% of GDP.[2] The running industry is not even high enough to score a 1/100 of a percent. If healthcare consumes so much of our world, why is it then that we focus so little attention on the specifics of quality or value or outcomes in healthcare?

Defining Quality, Value, and Outcome Measures

This became particularly obvious when working with the Oncology Medical Home Steering Committee and its objective of defining 16 quality, value, and outcomes measures for cancer care. This cross-section and balanced approach to defining key determinants to patient care, resource utilization, survivorship, and end-of-life care may prove challenging, but its time is past due. For example, as an outdoor enthusiast my hope is that I will be called home while running, fishing, or simply walking on a trail. For a cancer patient the hope is that they may leave this earth among family or friends and surrounded by a known and friendly environment—peacefully and quietly. Dying at home would seem to be the choice for all, if we had a choice. And there is no better indicator of the quality of life, at end of life, than the place of death. However, it seems that the national death registry does not record a "place" of death. The standard death certificate includes the following choices for place of death: "Hospital inpatient, ER/Outpatient or DOA; Nursing home, Residence or Other (Specify)." It would seem that it would be beneficial to include these data in the national death registry and to recognize same as a quality and value indicator for all of healthcare, not just cancer care. This seems to be an easy fix.

And somewhat related is the entire discussion surrounding end-of-life care discussions. The patient and their family need open and honest dialogue regarding their current status, their wishes, and how their wishes are to be carried out. This goes beyond the simple question of asking a patient if they are ready to meet their maker. One of several programs that attempt to remedy this issue is the "5 Wishes" program.[3] This program asks 5 probing questions regarding assigning decision makers, medical treatment preferences, preferred comfort levels, preferences on interactions with others, and last wishes. This program provides specific guidance on how to conduct these conversations. Dr John Sprandio (Pennsylvania) and Dr John Fox (Michigan) have indicated that when these discussions occur, and at the right time, patients have made decisions to discontinue aggressive cancer treatment. The end result is more comfortable end-of-life care. Although some patients (or family members) may resist these discussions, they should be required for any healthcare team charged with managing any terminal disease. When done properly, the door is left open for miracles, but the patient and family are able to make informed decisions regarding their care. Electronic medical record vendors will need to enhance their data capture fields from a simple "Advanced directive on file – Y or N" to a more detailed and comprehensive approach to this question if we are to raise the bar in care and compassion. There should be similar guidelines for the specifics of care plans and cancer survivorship plans.

Another milestone by the COA Oncology Medical Home Steering Committee was the endorsement that all cancer care providers should calculate their own 5-year survival rates for breast, colon, and lung cancers. This is completely logical and is a measurement whose time has come. As a former manager of a cancer center, I often wondered what I would say when asked for our own 5-year survival rate for stage 3 breast cancer. It would seem to be a logical and reasonable question but one that currently has no answer—at least not for an individual cancer center. "Survival" rates, when they are the only measure, are not necessarily a good indication of quality, particularly if a patient is being kept alive through artificial means and against the wishes of the patient or family. But, when combined with other standards and educational requirements, this information can be very helpful to the patient and their families in planning and in the celebration of significant milestones.

Overutilization of Hospital Services

One of the more elusive measures but one that has great significance in the value department is the use, or overuse, of hospital services. Some patients and healthcare providers are quick to utilize these expensive inpatient, outpatient, or emergency department (ED) resources over a less expensive setting such as the exam or procedure room of their medical home. Governmental and commercial payers all agree that the overuse of these resources represents a significant expense and an opportunity to realize savings in time and dollars to the payer and patient. The challenge with curbing this misuse of resources is that the person that should know of these encounters, the patient's medical home physician, does not always know when they occur. The hospital staff will be the first to know, the patient's payer may be the second to know, but the person that should know first, the patient's physician, may never know if or when this event occurs. Some commercial insurance companies are providing financial incentives to curb unnecessary ED visits or hospitalizations. This is why the COA OMH Steering Committee has endorsed this measure. Perhaps we need to revise this notion of "precertification" and insert the patient's medical home provider as the "mother may I" authority before these services are rendered. This procedural change would allow the patient's main care team to intervene with, hopefully, a more efficient solution. and it would also assist in nurturing the relationship between the patient and their medical home physician. Only then will we be able to measure and benchmark the utilization of these valuable resources and reward those care teams that use them appropriately.

AJMC.com Scan for additional content.

Robert Gamble talks about the challenges payers and providers face in oncology management ()

Applying Our Own "Golden Rule"

Other industries seem to have a head start on defining quality statements. Healthcare, and particularly cancer care, seems to be the last industry to define, measure, benchmark, and promote quality, value, and positive outcomes. Perhaps it is because we have been busy taking care of others that we have not been able to focus on such a mammoth undertaking. Now may be the time to apply our own "Golden Rule" to measuring quality and value in cancer care. After all, and as I am sometimes reminded, there is more to life than running and fishing.

Funding Source: None.

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

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

References

1. Healthcare in the United States. http://en.wikipedia.org/wiki/Health_care_in_the_United_States. Accessed January 3, 2013.

2. OECD. StatExtracts. http://stats.oecd.org/Index.aspx?DatasetCode=SNA_TABLE1. Accessed January 3, 2013.

3. Aging with Dignity website. www.agingwithdignity.org/five-wishes.php. Accessed January 3, 2013.

A One-Stop App

for Managed Care Professionals

Now Available!

All our monthly content in one place!

Download the *AJMC* iPad edition for full access to our content, such as:

- Print issue
- Web exclusives
- eAppendices
- Audio summaries

THE AMERICAN JOURNAL OF MANAGED CARE®

www.ajmc.com

Available on the App Store

THE AMERICAN JOURNAL OF MANAGED CARE

Searching for Clinical and Economic Value in Pancreatic Cancer

Marj P. Zimmerman, MS, BS Pharm; and Stanton R. Mehr

Pancreatic cancer is an extremely aggressive tumor type that continues to carry a dismal prognosis. Research regarding the cause of the cancer has continued, but important breakthroughs have been slow in coming. Additionally, pancreatic tumors demonstrate a resistance to chemotherapy, which has contributed to clinicians' frustration in obtaining remission, or even a firm foothold in managing it. This may also be related to the relatively late stage of the tumor at the time of diagnosis. Therefore, early diagnosis and the future discovery of an effective screening method could change the clinical picture and alter the search for value in managing this deadly cancer.

Mortality Increasing Unlike for Other Cancers

Death rates for most cancers have trended downward over the past 10 years; however, this has not been the case for pancreatic cancer. The incidence rate has increased by 0.9% per year in Caucasian men and women and African American men, while remaining stable in all others.[1] The **Table** illustrates the likelihood of developing pancreatic cancer over one's lifetime.[1] The majority of patients (74%) diagnosed will die within 1 year of diagnosis, whereas only 6% will survive for 5 years—this is the lowest relative survival of any cancer tracked by the American Cancer Society and the National Cancer Institute. Patients' average life expectancy after diagnosis of metastatic disease is only 5 to 7 months.[2] It is not one of the top 5 cancers in men or women in terms of incidence, yet it is the fourth leading cause of cancer death among men and women. More than 45,000 Americans will be diagnosed with pancreatic cancer in 2013, and over 38,000 will die this year.[1]

The incidence of pancreatic cancer increases with age, with the median age at diagnosis being 71 years. More men than women are diagnosed with the disease.[1]

Pancreatic cancer typically refers to a ductal adenocarcinoma (exocrine pancreatic cancer). A less common type is a neuroendocrine tumor (endocrine pancreatic cancer). The public profile of pancreatic cancer has been raised in recent years with the chronicled cases of Patrick Swayze (who had exocrine pancreatic cancer) and Steve Jobs (who had endocrine pancreatic cancer).[3] In fact, the dire prognosis for patients with pancreatic cancer has driven people like Jobs to seek unorthodox treatment and unproven therapies.

Patients with pancreatic neuroendocrine tumors have a somewhat better median overall survival than those with ductal adenocarcinomas. Unfortunately, the incidence of these tumors appears to be increasing.[4]

The cause(s) of pancreatic cancer are unknown. Family history is a positive risk factor and is identified in 5% to 10% of those diagnosed; the risk increases as the number of family members diagnosed with the disease increases. Smoking is also a risk factor, with a 2.5% to 3.6% increase in risk compared with non-smokers. As the number of life-years of smoking increases, so does the risk for pancreatic cancer.[5] Other potential risk factors include age; obesity; alcohol use; consumption of red and processed meat, and fructose sweeteners; chronic pancreatitis; diabetes; chronic infections (eg, hepatitis B virus, hepatitis C virus, and *Helicobacter pylori*); some surgeries (eg, partial gastrectomy, cholecystectomy); cystic fibrosis; and periodontal disease.[1]

Pancreatic cancer is not one of the top 5 cancers in men or women in terms of incidence, yet it is the fourth leading cause of cancer death among men and women.

Pancreatic cancer is usually not detected or diagnosed in the early stages of the disease, as there are no specific symptoms. Symptoms that bring patients to the physician's office include: nausea, vomiting, abdominal discomfort, abdominal pain that is localized to the tumor area, anorexia, weight loss, generalized weakness, and fatigue. The majority of the tumors develop in the head of the pancreas, which leads to obstructive cholestasis, rather than the tail of the pancreas. Overall, most tumors are found when only about 15% to 20% of patients are still candidates for surgery.[1,5]

Table. Probability (%) of Developing Pancreatic Cancer Over Selected Age Interval by Gender (2007-2009)

Age (y)	Men	Women
0 to 39	0.01 (1 in 9746)	0.01 (1 in 7479)
40 to 49	0.05 (1 in 2063)	0.04 (1 in 2475)
50 to 59	0.18 (1 in 563)	0.12 (1 in 843)
60 to 69	0.41 (1 in 241)	0.30 (1 in 335)
70 to 79	0.65 (1 in 155)	0.56 (1 in 179)
Lifetime risk	1.48 (1 in 67)	1.45 (1 in 69)

Source: Reprinted with permission from American Cancer Society. Cancer Facts & Figures 2013. Atlanta: American Cancer Society; 2013.[1]

As would be expected, costs for treating patients who undergo surgery are greater than costs for patients who have nonresectable tumors (either locoregional or metastatic). A Surveillance, Epidemiology, and End Results (SEER) Medicare database study that included patients diagnosed between 2000 and 2007 found the mean total costs for those 3 patient groups to be $134,000 (surgical candidates), $65,300 (patients with locoregional tumors), and $49,000 (patients with metastatic disease), with an average cost of $61,700. The largest portion of the costs was related to hospitalizations and cancer-related procedures (**Figure**).[6] Undoubtedly, improved treatment strategies may increase the cost of treating patients with pancreatic cancer by increasing their lifespans.

Genetics and Biomarkers

Pancreatic cancer is genetically heterogeneous. One study analyzing 24 tumors found 63 genetic abnormalities in each tumor that were believed to be likely relevant for the disease. It has been determined that there are always at least 1 or more genetic defects involving 4 genes in patients with pancreatic cancer.[5] Recent research has determined that germline mutations in *BRCA1* and *BRCA2* predispose women to pancreatic cancer, doubling their risk for developing it. The 5-year survival for these individuals was no greater than 5%.[7]

Epidermal growth factor receptor (*EGFR*) overexpression has been identified in 40% to 65% of pancreatic tumors. This overexpression leads to tumors being resistant to chemotherapy and an even poorer prognosis.[8] Since pancreatic tumors vary so much between patients, a highly individualized approach to treating the disease will probably be needed to improve patient outcomes.[9]

Currently, only 1 biomarker is approved by the US Food and Drug Administration for pancreatic cancer, serum Ca-19-9 (carbohydrate antigen 19-9, also known as cancer antigen-GI and CA-GI).[10] This marker is useful for identifying the tumor location, stage, and resectability.[11] However, not all pancreatic tumors produce Ca-19-9; therefore, it is not sensitive or specific enough to be used as a screening test.[1,12] However, the test does have value for evaluating effectiveness of treatment and early detection of recurrent disease.[5]

Other frequently used tests include endoscopic ultrasound, helical computed tomography, magnetic resonance imaging, and endoscopic retrograde cholangiopancreatography. To confirm the diagnosis, fine-needle aspiration biopsy is standard procedure.[1,13]

Staging of Pancreatic Cancer

Staging of the disease guides the type of treatment that will be the most effective. The 4 stages associated with pancreatic cancer are differentiated by the

location of the tumor and whether it has spread to lymph nodes and distant organs. Stage I indicates that the tumor is restricted to the pancreas, and stage IV describes cancer that has spread to a distant organ, such as the liver or lungs. Patients with stage III or IV tumors are generally not candidates for surgical resection, and this comprises about 80% of patients.[13,14] The lethality of this cancer in late stages cannot be overemphasized; survival is somewhat greater when diagnosed at an earlier stage. When a patient has surgery after being diagnosed with stage I or stage II cancer, the 5-year survival is 20% to 25%, whereas a patient diagnosed with stage IV cancer has a 5-year survival that is below 1%.[1,15]

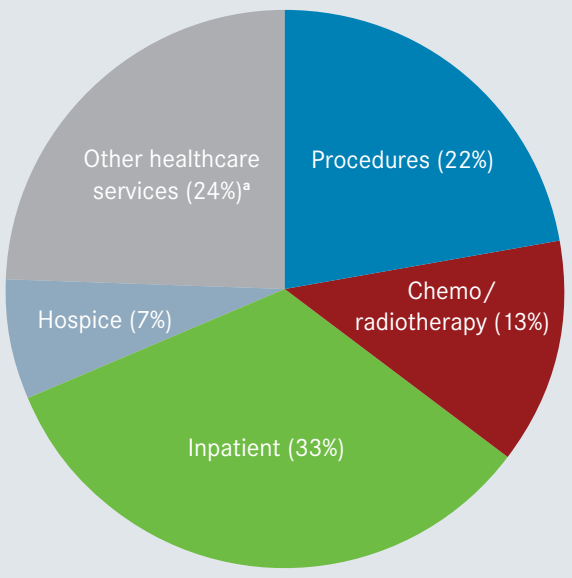
Treatment Options

Surgery is the only treatment option that can cure early-stage disease. However, a small percentage of patients present with stage I pancreatic cancer, because of the difficulty in diagnosing it. Surgical procedures most commonly performed include cephalic pancreatoduodenectomy (also known as the Whipple procedure), distal pancreatectomy, and total pancreatectomy. Predictors of improved survival include younger age and early-disease stage.[5,16] After surgery, adjuvant chemotherapy either alone or in combination with radiation therapy has been shown to improve survival. Neoadjuvant therapy, both chemoradiation or chemotherapy in combination or alone, are also options, especially when the patient has locally advanced or borderline rescectable disease. In patients undergoing surgery, the chemotherapy regimens initiated after the surgery usually include gemcitabine, 5-fluorouracil (5-FU) with leucovorin, or capecitabine.[14]

Since surgery for pancreatic cancer can involve several organs in the digestive system in addition to an already diseased organ, several potential morbidities should be considered. Up to 80% of patients undergoing surgical procedures for pancreatic cancer will require oral pancreatic enzyme replacement therapy (PERT). The dose of lipase required usually ranges from 160,000 to 400,000 units daily. A proton pump inhibitor may be added to improve the efficacy of the PERT, if there is adequate gastric acid secretion.[17] Since at least a portion of the pancreas is removed during surgery, the body's ability to produce insulin is compromised. As a result, up to 50% of patients develop diabetes and require insulin therapy postsurgery.[18] Other complications observed after surgery include gastroparesis, dumping syndrome, and vitamin and mineral deficiencies.[19]

For the majority of patients whose tumor is not resectable, the therapeutic options are chemoradiation and/or chemotherapy. Gemcitabine has been the mainstay of therapy since the late 1990s, when the drug was shown to increase median survival to 5.7 months compared with 4.4 months for those taking 5-FU (P = .0025), but the 1-year survival was worth noting (18% versus 2%, respectively).[20] Capecitabine is a pro-drug of 5-FU, and it has also demonstrated benefit in treating patients with pancreatic cancer.[21] A combination therapy regimen, FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin), was compared with gemcitabine in patients with stage IV metastatic disease that involved up to 6 distal sites. The combination therapy group showed an improved median overall survival (11.1 vs 6.8 mo, respectively; P <.0001). Median progression-free survival was also longer in the combination therapy group (6.4 vs 3.3 mo, respectively; P <.001).[22] Targeted *EGFR* therapy using erlotinib plus gemcitabine led to a marginally longer overall survival than gemcitabine alone (6.2 vs 5.9 mo, respectively; P = .038).[23]

Figure. Breakdown of Mean Direct Medical Costs for All 3 Patient Groups



[a]Other healthcare services includes outpatient care and physician services.
Source: Adapted with permission from O'Neill CB, Atoria CL, O'Reilly EM, et al. Costs and trends in pancreatic cancer treatment. *Cancer*. 2012;118(20):5132-5139.[6]

Cost Considerations

Since pancreatic cancer is such a devastating disease, strategies for screening individuals at high risk would be beneficial. Two cost-effectiveness studies of screening high-risk individuals led researchers to conclude that early cancer can be detected by screening; however, until new biomarkers with high specificity and sensitivity become available, this strategy may not be cost-effective.[24] Owing to the poor outcomes of patients with pancreatic cancer, the evaluation of cost-effective treatment strategies remains challenging. Alas, the survival of these patients is consistently short, and expressing incremental cost-effectiveness ratios (ICERs) in terms of years yields inadequate comparisons. For this reason, ICERs for pancreatic cancer interventions are often expressed in quality-adjusted life-months (QALMs), not life-years.

A recent review examined 6 treatment strategies: no treatment, radiotherapy only, chemotherapy only, chemotherapy plus radiotherapy, surgery alone, and surgery plus adjuvant therapy. The groups having surgery plus adjuvant therapy, chemotherapy alone, and no treatment were the only groups that were considered cost-effective. An ICER of $7663 per QALM was seen in the surgery plus adjuvant therapy group compared with the no-treatment group, which was primarily related to an increase in survival. Of note was that the ICER was most favorable in high-performing healthcare centers versus low-performing centers ($5991/QALM vs $9144/QALM, respectively). This indicates that decreasing costs will be related to improved therapies and utilizing high-performing care centers for providing the treatments.[25]

Another study examined the cost-effectiveness of gemcitabine monotherapy, gemcitabine plus conventional radiotherapy, gemcitabine plus intensity-modulated radiotherapy (IMRT), and gemcitabine with stereotactic body radiotherapy (SBRT). The SBRT group had better results both clinically and economically than each of conventional radiotherapy and SBRT groups, respectively, but only produced an increase of 0.20 quality-adjusted life-years (QALYs), at an incremental cost of $13,700 compared with gemcitabine alone. Using a willingness to pay of $50,000 per QALY as the threshold for cost-effectiveness, the probability of cost-effectiveness was 78% for gemcitabine monotherapy and 21% for SBRT, while at a willingness-to-pay threshold of $200,000 per QALY, the probability of cost-effectiveness for SBRT was 73%.[26]

Another type of cost strategy evaluation was undertaken that determined the budget impact of adding erlotinib to gemcitabine therapy in patients with nonresectable pancreatic cancer. The budget impact was $0.02 per member per month; this small amount was primarily the result of the low incidence of pancreatic cancer among the hypothetical managed care organization of 500,000 members. It would be difficult to deny patients the additional drug being added to a gemcitabine regimen even with limited survival benefits.[27]

Both the National Cancer Institute (NCI) and pharmaceutical companies are investigating new modalities for treating pancreatic cancer. The NCI has increased its budget for this disease by more than 50% since 2000. Yet, the complexity and variability of each tumor continues to challenge clinical treatment. As we learn more about the genetic makeup of pancreatic cancer, it will undoubtedly lead to new therapies, new combination therapy regimens, and biomarkers that will aid in the detection and monitoring of therapy. These advances will hopefully translate into better patient outcomes and economically sound treatment strategies. **EBO**

Funding Source: None.
Author Disclosures: Mr Mehr reports receiving payment for involvement in the preparation of this article. Ms Zimmerman reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.
Authorship Information: Concept and design (SRM); acquisition of data (MPZ, SRM); analysis and interpretation of data (MPZ, SRM); drafting of the manuscript (MPZ, SRM); critical revision of the manuscript for important intellectual content (MPZ, SRM); and supervision (SRM).

References

1. American Cancer Society. Cancer Facts & Figures 2013. Atlanta: American Cancer Society; 2013.
2. Pancreatic Cancer Facts 0212. Pancreatic Cancer Action Network. www.pancan.org/section_get_involved/advocate/downloads/Pancreatic%20Cancer%20Facts%20June%202012.pdf. Accessed February 5, 2013.
3. Begley S. Jobs's unorthodox treatment. The Daily Beast. October 2011. www.thedailybeast

THE AMERICAN JOURNAL OF MANAGED CARE

.com/articles/2011/10/05/steve-jobs-dies-his-unorthodox-treatment-for-neuroendocrine-cancer.html. Accessed February 5, 2013.
4. Halfdanarson TR, Rabe KG, Rubin J, et al. Pancreatic neuroendocrine tumors (PNETS): incidence, prognosis and recent trend toward improved survival. *Ann Oncol.* 2008;19(10):1727-1733.
5. Hidalgo, M. Pancreatic cancer. *N Engl J Med.* 2010;362(17):1605-1607.
6. O'Neill CB, Atoria CL, O'Reilly EM, et al. Costs and trends in pancreatic cancer treatment. *Cancer*. 2012;118(20):5132-5139.
7. Iqbal J, Ragone A, Lubinski J, et al. The incidence of pancreatic cancer in BRCA1 and BRCA2 mutation carriers. *Br J Cancer*. 2012;107(12):2005-2009.
8. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 2007;25(15):1960-1966.
9. Michl P, Gress TM. Current concepts and novel targets in advanced pancreatic cancer. *Gut*. 2013;62(2):317-326.
10. Fong ZV, Winter JM. Biomarkers in pancreatic cancer: diagnostic, prognostic, and predictive. *Cancer J*. 2012;18(6):530-538.
11. Molina V, Visa L, Conill, et al. Ca 19-9 in pancreatic cancer: retrospective evaluation of patients with suspicion of pancreatic cancer. *Tumour Biol.* 2012;33(3):799-807.
12. CA 19-9. Lab test online. http://labtestsonline.org/understanding/analytes/ca19-9/tab/test. Accessed February 5, 2013.
13. What you need to know about cancer of the pancreas. National Cancer Institute. July 2010. www.cancer.gov/cancertopics/wyntk/pancreas/page1/AllPages. Accessed February 4, 2013.
14. NCCN Clinical practice guidelines in oncology: pancreatic adenocarcinoma. V.2.2012. National Comprehensive Cancer Network. www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed February 4, 2013.
15. Billmoria KY, Bentrem DJ, Ko CY, et al. Validation of the 6th edition EJCC pancreatic cancer staging system. *Cancer*. 2007;110(4):738-744.
16. Shaib Y, Davila J, Naumann C, et al. The impact of curative intent surgery on the survival of pancreatic cancer patients: a U.S. population-based study. *Am J Gastroenterol*. 2007;102:1377-1382.
17. Dominguez-Munoz, JE. Pancreatic enzyme replacement therapy: exocrine pancreatic insufficiency after gastrointestinal surgery. HPB (Oxford). 2009:11(suppl 3):3-6.
18. Tran TCK, van Lanschot JJB, Bruno MJ, et al. Functional changes after pancreatoduodenectomy: diagnosis and treatment. *Pancreatology*. 2009;9(6):729-737.
19. Decher N, Berry A. Post-whipple: a practical approach to nutrition management. Practical Gastroenterology. www.medicine.virginia.edu/clinical/departments/medicine/divisions/digestive-health/nutrition-support-team/nutrition-articles/Decher_Berry_Aug_12.pdf. Published August 2012. Accessed February 13, 2013.
20. Burris HA III, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol.* 1997;15(6):2403-2413.
21. Warsame R, Grothey A. Treatment options for advanced pancreatic cancer. *Expert Rev Anticancer Ther*. 2012;12(10):1327-1336.
22. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817-1825.
23. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 2007;25(15):1960-1966.
24. Stoita A, Penman ID, Williams, DB. Review of screening for pancreatic cancer in high-risk individuals. *World J Gastroenterol*. 2011;17(19):2365-2371.
25. Abbott DE, Merkow RP, Cantor SB, et al. Cost-effectiveness of treatment strategies for pancreatic head adenocarcinoma and potential opportunities for improvement. *Ann Surg Oncol.* 2012;19(12):3659-3667.
26. Murphy JD, Chang DT, Abrelson J, et al. Cost-effectiveness of modern radiotherapy techniques in locally advanced pancreatic cancer. *Cancer*. 2012;118(4):1119-1129.
27. Danese MD, Reyes C, Northridge K, et al. Budget impact model of adding erlotinib to a regimen of gemcitabine for the treatment of locally advance, nonresectable or metastatic pancreatic cancer. *Clin Ther*. 2008;30(4):775-784.

Payer Perspective
Interview With Irwin W. Tischler, MD

EBO: **Why is pancreatic cancer such a difficult problem today? Do we have sufficient information on its risk factors to be of use in prevention?**
Dr Tischler: Pancreatic cancer is the fourth-most common cause of cancer-related deaths in the United States. There is little doubt that there are risk factors associated with pancreatic cancer. These include cigarette smoking, heavy alcohol intake, exposure to certain occupation-related chemicals, and obesity. Chronic pancreatitis has also been identified as a risk factor. A recent study demonstrated a 7-fold increase of pancreatic cancer for patients with a history of pancreatitis, and clinical studies are evaluating pancreatic cancer's relationship with other risk factors. Truly familial pancreatic cancer is uncommon. However, there may be a genetic predisposition in up to 10% of patients with pancreatic cancer. There is also an increase of pancreatic cancer in families who have the BRCA2 gene mutation.

EBO: **What do you see as the best value for our efforts to prevent, treat, or manage pancreatic cancer today?**
Dr Tischler: I believe our best efforts lie in educating our customers about their risk factors and how those risks can be reduced by changing lifestyle behaviors.

EBO: **Pancreatic cancer is usually detected or diagnosed in the latter stages of the disease. What can health plans do to help improve this situation or is this more of an issue requiring better provider education?**
Dr Tischler: It is unclear whether screening high-risk individuals is beneficial. Studies are ongoing in an effort to answer this question.

EBO: **With regard to the direct costs of treating the disease, surgical procedures and hospital stays are responsible for the lion's share (22% and 33%, respectively). Chemotherapy and radiotherapy account for only 13% combined. Do you expect that the chemotherapy costs will increase as more effective treatments are introduced?**
Dr Tischler: The overwhelming share of costs do relate to surgical procedures, including the cost of inpatient hospital stays. Mortality in the United States for pancreatic cancer has not changed much over the past 20 years, despite the introduction of more chemotherapy drug combination treatments. Overall, costs likely will continue to increase as newer chemotherapy agents become available, especially the targeted agents that are being used to treat many other malignancies.

EBO: **Do you think that other treatment-associated costs will become major contributors to this scenario in the future (eg, pancreatic enzyme replacement or biomarker testing)?**
Dr Tischler: Biomarker, molecular profiling, and gene array studies are currently in progress, and I believe this is the future—not only for pancreatic cancer, but for managing other malignancies as well. The results of these studies may enable us to take a novel and personalized approach to treat specific molecular targets that can be identified, and that will be predictive of chemotherapy sensitivity to treat pancreatic and other malignancies.

EBO: **In terms of pancreatic cancer (or perhaps all cancers), what, if any, clinical guidelines do you encourage oncologists to follow?**
Dr Tischler: Cigna encourages doctors who are treating our customers to follow evidence-based guidelines published by the NCCN and ASCO (American Society of Clinical Oncology). Cigna uses these guidelines to develop our coverage policies for pancreatic cancer and other malignancies.

EBO: **Because of the limited success with current treatments of patients with pancreatic cancer, are you perhaps more lenient in your approval of investigational treatments?**
Dr Tischler: Cigna covers experimental treatments for pancreatic cancer if the treatment is being done in conjunction with a listed clinical trial.

EBO: **Where do you expect the next big leap in pancreatic cancer management?**
Dr Tischler: I believe the next big leap, not only for pancreatic cancer but for all malignancies in general, will occur once we further unravel genetic and tumor-specific markers. Hopefully, this will enable oncologists to deliver personalized, effective therapy for all cancers.

Dr Tischler is national medical director for oncology at Cigna in Philadelphia, PA.

THE AMERICAN JOURNAL OF MANAGED CARE

PRECISION HEALTH ECONOMICS

P R E S E N T

Patient-Centered Diabetes Care

Future Directions

June 20, 2013
University of Chicago
Chicago, IL

Panelists

Dana Goldman, PhD
Director
Leonard D. Schaeffer Center for Health Policy and Economics
University of Southern California

Anne Peters, MD, CDE
Director
Clinical Diabetes Program
University of Southern California

Amitabh Chandra, PhD
Director of Health Policy Research
Harvard University

Anupam Jena, MD, PhD
Assistant Professor of Health Care Policy
Harvard Medical School

Michael E. Chernew, PhD
Professor of Health Care Policy
Harvard Medical School

Peter Huckfeldt, PhD
Professor
Pardee RAND Graduate School

Darius Lakdawalla, PhD
Director of Research
Leonard D. Schaeffer Center for Health Policy and Economics
University of Southern California

William H. Herman, MD, MPH
Director
Michigan Diabetes Research and Training Center
University of Michigan

Rebecca W. Killion, MA
Director
Professional Development
McKenna Long & Aldridge

Albert Tzeel, MD, MHSA, FACPE
National Medical Director
HumanaOne & KMG

Wade M. Aubry, MD
Associate Clinical Professor
Department of Medicine
Philip R. Lee Institute for Health Policy Studies
University of California, San Francisco

Jan Berger, MD, MJ
President & CEO
Health Intelligence Partners

Tomas Philipson, PhD
Daniel Levin Chair in Public Policy
Irving B. Harris Graduate School of Public Policy Studies
The University of Chicago

Deneen Vojta, MD
Senior Vice President
Business Initiatives and Clinical Affairs
UnitedHealth Group
Chief Clinical Officer
Diabetes Prevention and Control Alliance

Hear the leaders in diabetes discuss the issues and concerns facing payers and providers, including:

- **Individualized Treatment and Improving Outcomes: A Provider Panel Discussion**
- **The Impact of Patient Behavior on Quality of Care and Outcomes**
- **Meeting the Clinical and Social Needs of Patients With Diabetes: Payer Perspectives**

Register Now for the Best Price!

Date Purchased	Price
April 1 through April 30	$200
May 1 through May 31	$300
After May 31	$400

www.ajmc.com/meetings/diabetes

THE AMERICAN JOURNAL OF MANAGED CARE

The Future of Melanoma Treatment

Michael M. Mohundro, PharmD; and Alexis Horace, PharmD

According to the National Cancer Institute's Surveillance Epidemiology and End Results data, melanoma of the skin was estimated to be the cause of death in almost 10,000 people in 2012.[1] Unfortunately, melanoma incidence has been on the rise in the United States since 1981, with annual increases of almost 3%; however in white women under the age of 44 years, the increase has been double that, at 6.1%. The upward trend in this population may be due to the increased popularity of tanning bed use.[2]

Currently there are 5 types of treatments available to patients diagnosed with melanoma. The treatment types are surgery, chemotherapy, radiation, biologic therapy, and targeted therapy.[3] Melanoma is classified as a chemotherapy-resistant tumor; however, a response rate of 10 to 15 percent has been noted with certain single agents. Dating back to 1972, the gold standard for treatment of metastatic melanoma has been dacarbazine.[4] Drugs currently approved by the US Food and Drug Administration (FDA) for treatment of melanoma include aldesleukin, dacarbazine, ipilimumab, and vemurafenib.[5] This article will explore pharmacologic agents currently being investigated for the treatment of melanoma.

Microtubule Inhibitor

nab-paclitaxel

Solvent-based taxanes have limited utility due to limited efficacy and high rate of toxicity. In addition to adverse effects from the taxane, patients often experience reactions to the solvent. Albumin-bound paclitaxel is a 130-nanometer albumin-bound (nab) particle formulation of paclitaxel which does not require the use of a solvent. Utilization of *nab*-paclitaxel over traditional paclitaxel has the advantage of being able to deliver a higher dose while decreasing the incidence of serious grade 3 or 4 side effects.[6] Further, the *nab*-Paclitaxel formulation does not have the same "allergic" potential as the solvent-based formulation.[6,7] Of particular note, the albumin-binding protein Secreted Protein, Acidic and Rich in Cysteine (SPARC) may play an important role in the effectiveness of *nab*-paclitaxel in melanoma. It is often overexpressed in a large number of malignancies, including melanoma, and is considered a poor prognostic indicator.[7] While the exact role in melanoma treatment has yet to be fully defined, the efficacy of *nab*-paclitaxel has been comparable to standard dacarbazine treatment and single-agent paclitaxel as well as other combination therapies.[7] In a recent phase II trial in combination with carboplatin in patients with unresectable stage IV melanoma, the *nab*-paclitaxel/carboplatin combination had a slight advantage in survival rate over ipilumimab.[6] However, the survival benefit was limited to the chemotherapy-naïve subgroup.[6] Several more phase II trials evaluating *nab*-paclitaxel in combination with either bevacizumab or other agents have been completed and results are pending.[6,8] Results of a phase III open-label, multicenter trial investigating *nab*-paclitaxel versus dacarbazine in treatment-naïve metastatic malignant melanoma demonstrated better median progression-free survival (PFS) and interim overall survival (OS) with *nab*-paclitaxel (PFS: 4.8 vs 2.5 months [hazard ratio (HR): 0.792, 95.1% confidence interval (CI): 0.631-0.992, *P* = .044], OS: 12.8 vs 10.7 months [HR: 0.831, 99.9% CI: 0.578-1.196, *P* = .094]).[9]

Plasmid/Lipid Complex Containing MHC I

Velimogene aliplasmid

Velimogene aliplasmid is a new form of immunotherapy for the treatment of metastatic melanoma. MHC class I and II expression is important for detection and lysis of foreign antigens by the immune system. Oftentimes, tumor cells go undetected by class I-restricted T cells by downregulating these processes.[10-12] Velimogene aliplasmid consists of a DNA plasmid, which hosts the genetic code for MHC class I proteins, HLA-B7, and B2-microglobulin, which improve expression of the HLA-B7 gene.[12] By encoding these 3 genes together, it provides several immune-stimulating features that increase the potential for tumor cell lysis. Several phase I studies have been conducted in small groups and demonstrated improved T-cell infiltration into tumor lesion, improved HLA-B7 surface expression, and promoted regression.[12,13] An unpublished phase III trial in 2001 compared velimogene aliplasmid combined with dacarbazine with dacarbazine alone in chemotherapy-naïve patients.[14] Response rates for dacarbazine were 11.6% and 13.2% for dacarbazine/velimogene aliplasmid. When comparing dacarbazine with dacarbazine/velimogene aliplasmid, survival durations were 9.24 months versus 10.75 months, respectively. Time to progression was 1.6 versus 1.9 months for dacarbazine and the combination. The authors concluded that velimogene aliplasmid did not increase clinical improvements beyond the standard of care. However, velimogene aliplasmid is currently being compared with dacarbazine alone in an ongoing phase III clinical trial investigating the safety/tolerability and OS rates of the 2 therapies.[15]

Vaccines

MAGE-A3 ASCI (astuprotimut-r)

Since therapeutic vaccination with dendritic cells (DCs) for melanoma was first proposed in the 1990s, knowledge has grown with regard to their development and efficacy.[16] With the boost from the recent FDA approval of sipuleucel-T in castrate-resistant prostate cancer, DC-based vaccinations remain a focused area of interest in solid tumors including melanoma.[16] While progress has been made in the understanding of DC-based vaccines, further study is needed in the hopes of realizing the dramatic results seen in animal models.[16,17] Several studies are currently recruiting participants to evaluate vaccine therapy, including an open-label, non-randomized phase I/II study investigating the effect of MAGE-3 in patients with stage IV cutaneous melanoma.[18] Another randomized phase II study is looking at the effectiveness of the vaccine in combination with IL-12 followed by daclizumab in patients with metastatic melanoma.[19]

Oncolytic Herpes Simplex VirusType 1(HSV-1) Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)

An oncolytic HSV-1 vaccine using GM-CSF to modulate antitumor immunity is being explored.[20,21] In addition to this cytokine-modified, cell-based vaccine activating the cytotoxic effects of macrophages to human melanoma cells, GM-CSF is a mediator for the maturation and mobility of DCs, and increases

Melanoma is classified as a chemotherapy-resistant tumor; however, a response rate of 10 to 15 percent has been noted with certain single agents.

Date Updated	Company/ Sponsor	Product	Mechanism of Action	Indication(s)	Stage(s)	License/ Partner(s)	PDUFA Date
11/26/12	Celgene	nab-paclitaxel (Abraxane)	Microtubule inhibitor	HER-2(+) BC; inflammatory BC (IV); mucinous BC (II); tubular BC (II/III)	Phase III	N/A	N/A
01/11/13	Vical	Velimogene aliplasmid (Allovectin-7)	Plasmid/lipid complex containing MHC-I	Metastatic melanoma (III/IV)	Phase III	N/A	N/A
02/28/13	GlaxoSmith Kline	Astuprotimut-R	MAGE-A3 vaccine	Metastatic/progressive/ unresectable melanoma	Phase I/II	N/A	N/A
06/01/12	BioVex Limited	talimogene laherparepvec (OncoVEX^{GM-CSF})	Oncolytic HSV-1 vaccine	Melanoma	Phase III	Amgen	N/A
02/21/13	Novartis	Nilotinib (AMN-107)	TKI	ALL; CML; melanoma	Phase II	N/A	N/A
10/01/12	AB Science	Masitinib (AB1010)	TKI	GI stromal tumors; metastatic melanoma; MM; MS; RA	Phase III	N/A	N/A
03/04/13	Genentech; Exelixis	GDC-0973; XL518	MEK inhibitor	Malignant melanoma	Phase III	Roche Group	N/A
01/08/13	Array Biopharma	MEK 162 (ARRY-438162)	MEK inhibitor	Metastatic/unresectable cutaneous melanoma	Phase III	Novartis	N/A
02/28/13	GlaxoSmith Kline	Trametinib (GSK1120212)	MEK inhibitor	Melanoma	Phase III	N/A	N/A
07/27/12	Pfizer	Ticilimumab; Tremelimumab (CP-675,206)	IgG2 monoclonal antibody	Advanced melanoma (IIIc/IV)	Phase II (Phase III no longer available)	N/A	N/A
02/28/13	GlaxoSmith Kline	Dabrafenib (GSK2118436)	Selective BRAF inhibitor	Melanoma	Phase III	N/A	N/A
02/22/13	Bristol-Myers Squibb	Anti-PD-L1 (BMS-936559; MDX-1195)	Anti-PD-L1 monoclonal antibody	CML; melanoma (III/IV); MM; (N)HL	Phase I	N/A	N/A
02/01/13	Bristol-Myers Squibb	Nivolumab (BMS-936558; MDX-1106)	Anti-PD-L1 monoclonal antibody	Metastatic melanoma; RCC; Squamous NSCLC	Phase III	N/A	N/A
01/04/23	Genta Incorporated	Oblimersen sodium (Genasense; GS3139)	Bcl-2 antisense oligodeoxynucleotide	Advanced melanoma; AML	Phase III	N/A	N/A

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; BC, breast cancer; CML, chronic myelogenous leukemia; GI, gastrointestinal; MM, multiple myeloma; MS, multiple sclerosis; (N)HL, (non)-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; PD, programmed death; RA, rheumatoid arthritis; RCC, renal cell carcinoma.

production of matrix metalloelastase, ultimately leading to the suppression of pulmonary metastases.[20] Treatment involves directly injecting the vaccine into the tumor, which avoids host immunity from destroying the virus.[21] A small phase II clinical trial examined the use of GM-CSF as adjuvant therapy in stage III and IV malignant melanoma.[22] The authors concluded that survival was significantly better for the overall patient population in the GM-CSF group ($P = .001$; $P = .04$ for stage III; $P = .001$ stage IV). Median survival increased approximately 25 months in treatment groups with minimal side effects noted. A current phase III study is examining the efficacy and safety of the oncolytic HSV1/GM-CSF vaccine compared with GM-CSF. The purpose is to investigate the overall survival (OS) rate.[23] Another phase III clinical trial is currently enrolling patients to investigate the safety of the vaccine over 12 months.[24]

Tyrosine Kinase Inhibitors

Nilotinib

Nilotinib is an orally bioavailable, small molecule tyrosine kinase inhibitor (TKI) that targets abl-kinases, c-KIT, and PDGFR. Currently, it is FDA approved for patients with chronic myeloid leukemia.[25,26] While KIT has been well established as a therapeutic target in cancer, there is limited research in the area of melanoma.[26] In preclinical trials, evidence has shown that melanoma cell lines containing KIT mutations had a favorable response to treatment with imatinib, which also targets c-KIT.[26] Additionally, phase II trials have demonstrated overall response rates of 16% to as high as 30.2% with imatinib. Common reactions to treatment have included alopecia, skin rash, and headache. Multiple studies are ongoing in melanoma to determine the value of treatment in melanoma, specifically with KIT mutations.[26] A phase II study evaluating nilotinib in patients with melanoma from sun-damaged skin

While it has been demonstrated in the early stages of melanoma that the immune system mounts a strong response, tumors ultimately develop mechanisms to evade detection and destruction.[16]

(continued on SP110

Patient Assistance NO

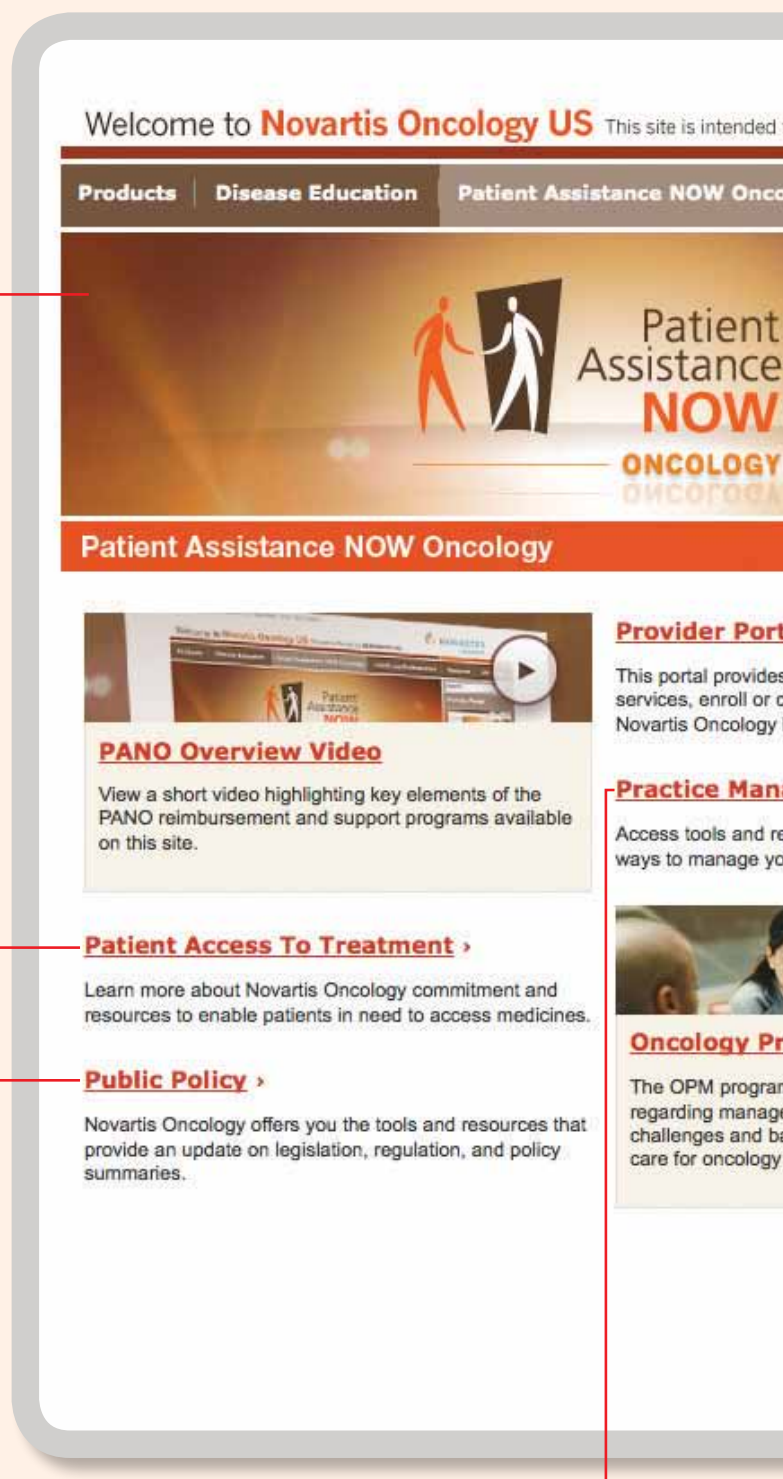
Our Patient Assistance Now Oncology (PANO) Web site makes it easy with all-in-one convenience providing simplicity, efficiency, and better access for you, your patients, and your oncology practice managers (OPMs).

Let's Get Started!

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

For Patient Care

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



What's New in Healthcare Reform?

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

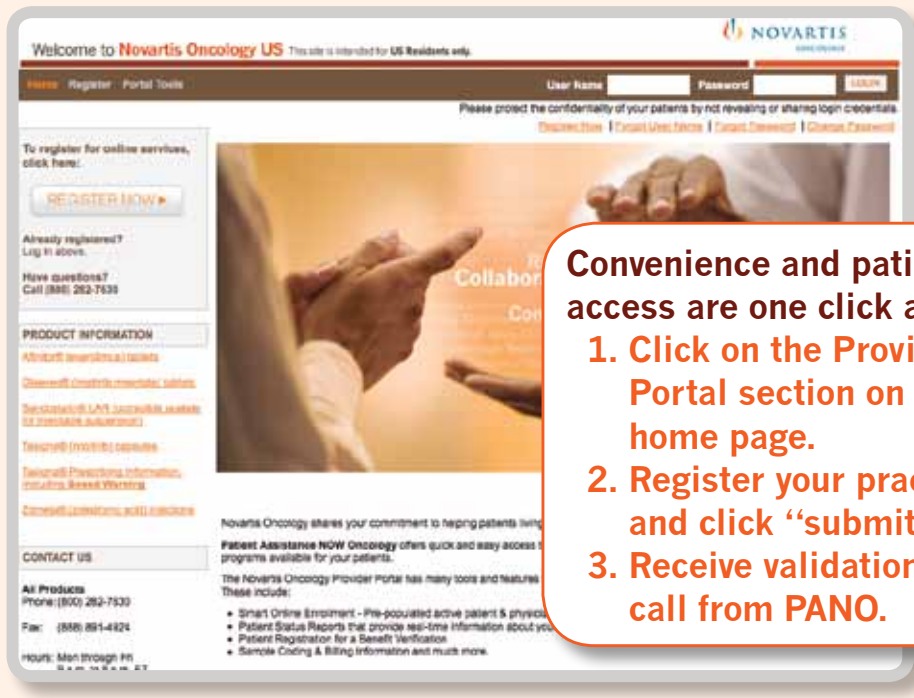
Patient Access SOS

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

Brought to you by the publisher of

THE AMERICAN JOURNAL OF MANAGED CARE

OW Oncology Mapped!®



Convenience and patient access are one click away:

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

What Can the Provider Portal Do for Me?

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

A Program Just for OPMs

A link to an OPM program that provides education and tools

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

Patient Assistance NOW Oncology
www.OncologyAccessNow.com

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

Patient Assistance NOW ONCOLOGY

Helping to make access to therapies easier

NOVARTIS ONCOLOGY

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

THE AMERICAN JOURNAL OF MANAGED CARE

(continued from SP107)

who did not respond to or could not tolerate treatment with another TKI is ongoing. Four other phase II studies investigating nilotinib in patients with melanoma are currently open to accrual.[27]

Masitinib

Masitinib, an orally bioavailable TKI, is being investigated for use in both human and veterinary medicine simultaneously.[28] This small molecule inhibitor of KIT, PDGFR (α+β), and Lyn has been conditionally approved by the FDA for use in dogs with cutaneous mast cell tumors.[29,30] Although no clinical data are available regarding human use of masitinib for melanoma treatment, preclinical data suggest patients carrying a c-KIT juxtamembrane (JM) mutation will respond.[28] One phase III study comparing masitinib with dacarbazine in patients with melanoma with a mutation in the JM domain of C-Kit is currently recruiting patients.[31]

MEK Inhibitors

GDC-0973

Mutations in proto-oncogene B-Raf (BRAF) are common in 40% to 60% of melanomas and the MAP/ERK kinase (MEK) pathway is a part of the mutation cascade.[32] GDC-0973 is a new and highly selective, small molecule MEK inhibitor being studied for its antineoplastic activity. Mutations in the MEK cascade contribute to increased cell proliferation, invasion, metastasis, angiogenesis, and inhibition of apoptosis.[33] Malignant melanomas commonly have single amino acid mutations (BRAF V600E) in a single loop of the kinase.[33] GDC-0973 binds to MEK1 and inhibits ERK2 phosphorylation, ultimately decreasing tumor growth.[34] Preclinical trials have shown that this novel agent in combination with vemurafenib and GDC-0941, a PI3K inhibitor, is effective in decreasing growth in those tumors harboring a BRAF mutation.[33,34] An open-label, dose escalation, phase I clinical trial is currently recruiting patients with BRAF V600E malignant melanoma to evaluate the safety, tolerability, and pharmacokinetics of GDC-0973.[35] Concurrently, a phase III clinical trial is also recruiting patients with untreated BRAF V600 mutations and unresectable, locally advanced metastatic melanoma to evaluate the safety and efficacy of vemurafenib compared with vemurafenib combined with GDC-0973.[36]

MEK162

MEK162 is another powerful inhibitor of MEK1 and MEK2. This novel agent is also being studied for inhibition of NRAS mutations. Research has shown that NRAS mutations are associated with a poor OS as well as the development of CNS metastases.[37] Preclinical trials using in vitro and in vivo studies have shown MEK162 inhibited growth of NRAS, Val600GLU BRAF-mutated melanoma.[32,38] Recently, MEK162 was investigated in an open label, phase II clinical trial. No patients had a complete response to therapy with MEK162. However, 20% of the NRAS-mutated melanoma group and 20% of the BRAF-mutated melanoma group had a partial response. The most common side effects included acneform dermatitis, rash, diarrhea, and increased creatine phosphokinase. Another phase II trial is in progress, which is assessing the safety and efficacy of MEK162 in malignant, cutaneous melanoma that has NRAS and BRAFV600 mutations.[39] Future studies include a phase Ib/II study assessing the use of LEE011 in combination with MEK162 and phase III study investigating efficacy of MEK162 versus dacarbazine for metastatic melanoma. Both studies have yet to recruit participants.[40,41]

Trametinib

Trametinib is another small-molecule, selective inhibitor of MEK1 and MEK2 that can be taken orally.[42] Trametinib has been shown to decrease cell proliferation and induce apoptosis.[43] In vitro evidence suggests trametinib in combination with a BRAF inhibitor increased rate of tumor-infiltrating lymphocytes in selected biopsy material. However, responses to the treatment varied and the authors were unable to definitively distinguish the role of MEK in the results.[44] A phase III clinical trial assessing survival benefit in patients with BRAF-mutated melanoma received either trametinib or chemotherapy (dacarbazine or paclitaxel). Median duration of PFS was 4.8 months in the trametinib group compared with 1.5 months in the chemotherapy groups (n = 322; P <.001).[45] An open-label, 2-stage phase II study examined trametinib in patients with BRAF-mutated cutaneous melanoma.[46] Patients were assigned to 2 cohorts: those previously treated with vemurafenib or dabrafenib (cohort A) or those previously treated with chemotherapy/or immunotherapy, but no BRAF treatment (cohort B). No cohort A patients had a confirmed clinical response; however, 20% experienced tumor reduction at the time of study cutoff. Out of cohort B, there was 1 complete response (2%) and 13 partial responses (23%), which resulted in a relative risk of 25% (95% CI, 14.1%-37.8%). Currently there are several phase II and III clinical trials actively recruiting patients to further research trametinib in treating melanoma.[47]

Many tumors, including melanoma, have been shown to selectively express PD-L1, making it an excellent therapeutic target.

IgG2 Monoclonal Antibody

Tremelimumab

While it has been demonstrated in the early stages of melanoma that the immune system mounts a strong response, tumors ultimately develop mechanisms to evade detection and destruction.[16] Immunosuppressive adaptations include induction of immune tolerance as well as resistance to cell death by activated effector arms of the immune system.[16,48] Under normal physiologic conditions, the immune system has checkpoints and feedback mechanisms that establish tolerance to self-antigens and prevent autoimmunity.[16] Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) is one of the molecules that assists in maintaining immune homeostasis by downregulating T-cell activation. In 2011, the FDA approved ipilimumab, the first monoclonal antibody (mAb) directed against CTLA-4. While only demonstrating modest results, it was the first drug treatment for melanoma to show a significant increase in OS.[16,49] Another anti-CTLA-4 mAb under development is tremelimumab, which also blocks CTLA-4 signaling and thus extends T-cell activation and stimulates T-cell proliferation.[16] By restoring T-cell mediated immunity, it increases the patient's ability to fight the tumor.[16] While early clinical trials with tremelimumab suggested favorable results, a subsequent randomized phase III trial was ended early after failing to show superiority to a standard of care chemotherapy regimen.[50] Additionally, there were serious autoimmune reactions including colitis, rash, and endocrinopathy.[16] Future analysis looks to study these agents in the adjuvant setting as well as in combination with other agents targeting BRAF and c-KIT mutations.[16]

BRAF Inhibitor

Dabrafenib

Dabrafenib is a reversible, selective inhibitor of BRAF Val600GLu. Very similar to vemurafenib in its mechanism of action and pharmacodynamics, it differs in the length of its half-life (5.2 hours vs 50 hours).[51] A phase II study used dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutation melanoma that had metastasized.[52] Patients were placed into one of 2 groups, those who had not received any local treatments (cohort A) and those who had progressive brain metastases after previous local treatments (cohort B). Patients with the Val600Glu mutation in cohort A had a 39.2% response rate (n = 74; 95% CI 28.0-51.2) and patients in cohort B had a 30.8% response rate (n = 65, 95% CI, 19.9-43.4); 95% CI, 19.9-43.4). For those with the Val600Lys mutation, response rates were 6.7% (n = 15; 95% CI 0.2-31.9) and 22.2% (n = 18; 95% CI 6.4-47.6) in cohorts A and B. Grade 3 adverse events occurred in 22% of the total patient population. The authors concluded that dabrafenib is active in treating metastatic brain melanoma and has an acceptable safety profile. Dabrafenib was further investigated in a phase III study which randomized patients with previously untreated stage IV or unresectable stage III BRAF-mutated melanoma to receive dabrafenib or dacarbazine.[53] Median PFS was 5.1 versus 2.7 months for dabrafenib compared with dacarbazine (HR 0.30; 95% CI 0.18-0.51; *P* <.001). Patients in the dabrafenib group had increased overall survival (HR 0.16, 95% CI 0.25-1.48). The most common adverse events listed for dabrafenib included fever, fatigue, arthralgia, and headache. Due to side effects, dose reductions occurred in 28% of patients. Currently, dabrafenib is being studied in a phase II clinical trial to further assess its safety and efficacy.[54] Simultaneously, a phase II clinical trial conducted in patients with BRAF-mutated metastatic melanoma of the brain is examining the overall intracranial response rate over approximately 15 years.[55] Other studies are also underway evaluating dabrafenib in melanoma.[56]

Anti–Programmed Death 1 Agents

Programmed death 1 (PD-1) protein and its ligand, PD-L1, play a critical role in melanoma's ability to escape the natural immune response.[48,57] In preclinical models, blockade of the

interactions between PD-1 and PD-L1 improved immunologic response and enhanced in vitro antitumor activity.[57] According to Zitvogel and Kroemer, the interaction between PD-1 and PD-L1 inhibits T lymphocyte proliferation, cytotoxicity, and cytokine release, induces apoptosis of tumor-specific T cells, and promotes the differentiation of CD4+ T cells into Foxp3-regulatory T cells as well as the resistance of tumor cells to CTL attack.[57] Unlike CTLA-4 ligands, many tumors, including melanoma, have been shown to selectively express PD-L1, making it an excellent therapeutic target.[57] Overexpression of PD-L1 can suppress cytokine production and cytolytic activity of tumor-infiltrating CD4+ and CD8+ T cells.[57]

BMS-936559

BMS-936559, formerly MDX-1105, is a human monoclonal antibody specific to PD-L1 (Anti-PD-L1 mAb) that inhibits the binding of PD-L1 to both PD-1 and CD80.[57] Results from a phase I clinical trial in patients with advanced cancer including metastatic melanoma indicated that treatment with BMS-936559 yielded a 6% to 17% objective response rate and that the effect on disease stabilization was prolonged at greater than or equal to 24 weeks.[57] Early evidence suggests that the adverse effect profile is more favorable than seen with anti-CTLA-4 treatments.[48,57] Grade 3 or 4 events occurred in 9% of the study population and were consistent with a mild autoimmune profile.[48,57] Curiously, there are currently no follow-up studies recruiting nor ongoing on the clinical trials website. There was a phase I anti-PD-L1 biomarker study for advanced melanoma listed, but it has a status of withdrawn with no reason given.[58]

Despite the limited and poor therapeutic options to date, a wide array of therapies are under development.

Nivolumab

On the other hand, nivolumab, which is an Anti-PD-1 mAb, has a wide array of studies either planned or ongoing.[59] While it is unclear why the focus has been shifted away from BMS-936559, it was observed in initial trials that the objective response rate was higher with nivolumab.[48]

Bcl-2 Inhibitor

Oblimersen Sodium

Oblimersen sodium is a new medication that downregulates the Bcl-2 protein and increases apoptosis of chemotherapy-treated human cancer xenografts.[60-62] Bcl-2 is an antiapoptotic protein that stops the release of cytochrome C, which is vital for triggering apoptosis of cancer cells.[60] Oblimersen consists of an 18-based phosphothiate antisense oglionucleotide, which binds to Bcl-2 mRNA and mediates its cleavage.[60] A phase I study comparing oblimersen/dacarbazine with dacarbazine alone demonstrated that patients in the oblimersen treatment arm had improved survival ($P = .007$) and increases in PFS ($P < .001$) over a minimum of 24 months. There were no increases in infections or bleeding events despite increases in neutropenia and thrombocytopenia with oblimersen. The purpose of another phase I trial in 2011 was to determine the safety and dose of oblimersen in combination with temozolomide and albumin-bound paclitaxel in patients with stage III or IV melanoma.[63] A total of 14 grade 3 and 4 adverse effects (fatigue, allergic reaction, neutropenia, thrombocytopenia, neuropathy, and hyponatremia) were recorded, but eventually resolved. The authors also reported complete response in 2 patients, and partial responses in 11 patients. A phase III, randomized, open-label, multicenter study comparing disease progression of patients treated with dexamethasone with or without oblimersen demonstrated no significant difference in response to TTP or objective response rate.[64] Oblimersen is currently being tested in a phase I trial combining it with *nab*-paclitaxel and temozolomide in patients with advanced melanoma.[65]

Conclusion

The management and treatment of patients with metastatic melanoma is quickly evolving. Despite the limited and poor therapeutic options to date, a wide array of therapies are under development. Research has advanced the understanding of the disease processes and we are gaining a better understanding of resistance mechanisms. Previously viewed as 1 disease, melanoma is now recognized as a heterogeneous mixture of cancer subtypes. Likewise, the traditional "one size fits all" model of treatment is no longer accepted as the most effective approach. Hydroxyurea, high-dose IL-2, and dacarbazine were the only drugs FDA approved for treating metastatic melanoma in 2011. As of today, ipilimumab and vemurafinib are FDA approved and there are numerous other agents in the pipeline. Further investigation is needed because these newer agents have had only a limited benefit, with overall survival still very low. Combining newer agents with established older therapies may have value in treating this complex disease state, but combinations of the newer medications may yield the synergy that is desperately needed to overcome the flat rate of survival. Along with some of the new breast cancer therapies, ipilumumab has put the cost-to-benefit argument directly in the national spotlight. Marginal gains in outcomes with increased toxicities does not make a good argument to payers. This is further aggravated in melanoma due to the relatively low number of cases annually and the cost of research and development: basic supply and demand. With these soaring costs of treatment and the burden on the healthcare system, ethical questions frequently enter the conversation. While certainly sharing the decision making and costs with the patient as well as educating the health providers helps, properly characterizing the patient's tumor is equally important. There is a big difference between blindly using a drug with little or no evidence that it will work and knowing that the tumor has the right markers for success. All things considered equal, the standard of care should likely be the first approach.

Funding Source: None.

Author Disclosures: None.

Authorship Information: Concept and design (MM); acquisition of data (MM, AH); analysis and interpretation of data (MM, AH); drafting of the manuscript (MM, AH); critical revision of the manuscript for important intellectual content (MM); statistical analysis; provision of study materials or patients; and obtaining funding.

References

1. SEER Stat Fact Sheets: Melanoma of the Skin. http://seer.cancer.gov/statfacts/html/melan.html. Accessed February 17, 2013.

2. Little EG, Eide MJ. Update on the current state of melanoma incidence. *Dermatol Clin.* 2012;30(3): 355-361.

3. Melanoma treatment. http://www.cancer.gov/cancertopics/pdq/treatment/melanoma/Patient/page4#Keypoint17. Accessed February 17, 2013.

4. s Yang AS, Chapman PB. The history and future of chemotherapy for melanoma. *Hematol Oncol Clin North Am.* 2009;23(3):583-597.

5. Drugs for melanoma. http://www.cancer.gov/cancertopics/druginfo/melanoma. Accessed February 17, 2013.

6. Kottschade LA, Suman VJ, Amatruda T 3rd, et al. A phase II trial of nab-paclitaxel (ABI-007) and carboplatin in patients with unresectable stage IV melanoma: a North Central Cancer Treatment Group Study, N057E(1). *Cancer.* 2011;117(8):1704-1710.

7. Hersh EM, O'Day SJ, Ribas A, at al. A phase 2 clinical trial of nab-paclitaxel in previously treated and chemotherapy-naive patients with metastatic melanoma. *Cancer.* 2010;116(1):155-163.

8. ClinicalTrials.gov website. http://www.clinicaltrials.gov/ct2/results?term=nab-paclitaxel+melanoma&Search=Search. Accessed March 2, 2013.

9. Hersh E, Del Vecchio M, Brown M, et al. Phase 3, randomized, open-label multicenter trial of nab-paclitaxel (nab-P) vs dacarbazine (DTIC) in previously untreated patients with metastatic malignant melanoma (MMM) [abstract]. *Pigment Cell Melanoma Res.* 25;836-903.

10. Natali PG, Nicotra MR, Bigotti A, et al. Selective changes in expression of HLA class I polymorphic determinants in human solid tumors. *Proc Natl Acad Sci.* 1989;86(17):6719-6723.

11. Van Duinen SG, Ruiter DJ, Broecker EB, et al. Level of HLA antigens in locoregional metastases and clinical course of the disease in patients with melanoma. *Cancer Res.* 1988;48(4):1019-1025.

12. Stopeck AT, Jones A, Evan M, et al. Phase II study of direct intralaesional gene transfer of Allovectin-7, an HLA-B7/B2-Microglobulin DNA-Liposome Complex, in patients with metastatic melanoma. *Clin Cancer Res.* 2001;7(8):2285-2291.

13. Stopeck AT, Hersh EM, Akporiaye ET, et al. Phase I study of the direct gene transfer of allogenic histocompatability antigen, HLA-B7, in patients with metastatic melanoma. *J Clin Oncol.* 1997;15:341-349.

14. Bedikian AY, Vecchio M. Alovectin-7 therapy in metastatic melanoma. *Expert Opin Biol Ther.* 2008;8(6):839-844.

15. ClinicalTrials.gov website. http://clinicaltrials.gov/show/NCT00395070. Accessed February 25, 2013.

16. Kirkwood JM, Butterfield LH, Tarhini AA, et al. Immunotherapy of cancer in 2012. *CA Cancer J Clin.* 2012;62(5):309-335.

17. Oshita C, Takikawa M, Kume A, et al. Dendritic cell-based vaccination in metastatic melanoma patients: phase II clinical trial. *Oncol Rep.* 2012;28(4):1131-1138.

18. ClinicalTrials.gov website. http://clinicaltri-

als.gov/ct2/show/NCT00074230?term=mage+melanoma&rank=17. Accessed February 25, 2013.
19. ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/show/NCT01437605?term=mage+melanoma&rank=8. Accessed February 25, 2013.
20. Chang EY, Chen CH, Hongxiu Jr, et al. Antigen-specific cancer immunotherapy using a GM-CSF secreting allogenic tumor cell-based vaccine. *Int J Cancer.* 2000;86:725-730.
21. Schmidt C. Amgen spikes interest in live virus vaccines for hard-to-treat cancers. *Nat Biotechnol.* 2011;29(4):295-296.
22. Spitler LE, Grossbard ML, Ernstoff MS, et al. Adjuvant therapy of stage III and IV malignant melanoma using granulocyte-macrophase colony-stimulating factor. *J Clin Oncol.* 2000;18(8):1614-1621.
23. ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/show/NCT00769704?term=oncovex&rank=3. Accessed February 23, 2013.
24. ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/show/NCT01368276?term=oncovex&rank=4. Accessed February 23, 2013.
25. Tasigna website.https://www.us.tasigna.com/health-care-professional/index.jsp?site=PC002491&source=01030&irmasrc=NA. Accessed March 1, 2013.
26. Cho JH, Kim KM, Kwon M, Kim JH, Lee J. Nilotinib in patients with metastatic melanoma harboring KIT gene aberration. *Invest New Drugs.* 2012;30(5):2008-2014.
27. ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/results?term=nilotinib+melanoma&Search=Search. Accessed February 25, 2013.
28. Masitinib scientific data for veterinary medicine. http://www.kinavet.com/file/Kinavet%20Scientific%20Data%20for%20Veterinary%20Medicine%20-%20July2011.pdf. Accessed March 2, 2013.
29. Kim EJ, Zalupski MM. Systemic therapy for advanced gastrointestinal stromal tumors: beyond imatinib. *J Surg Oncol.* 2011;104(8):901-906.
30. Kinavet-CA1 package insert. http://www.kinavet.com/file/Kinavet%20CA1%20package%20insert%20draft.pdf. Accessed March 1, 2013.
31. ClinicalTrials.gov.http://www.clinicaltrials.gov/ct2/show/NCT01280565?term=masitinib+melanoma&rank=1. Accessed March 4, 2013.
32. Ascierto PA, Schadendorf D, Berking C, et al. MEK162 for patients with advanced melanoma harbouring NRAS or VAL600 BRAF mutations: a non-randomized, open label phase 2 study [published online February 13, 2013]. *Lancet.*
33. Hoeflich KP, Merchang M, Orr K, et al. Intermittent administration of MEK inhibitor GDC-0973 plus PI3K inhibitor GDC-0941 triggers robust apoptosis and tumor growth inhibition. *Cancer Res.* 2011;72:210-219.
34. Baudy AR, Dogan T, Flores-Mercado JE, et al. FDG-PET is a good biomarker of both early response and acquired resistance in BRAF V600 mutant melanomas treated with vemurafenib and MEK inhibitor GDC-0973. *EJNMMMI Research.* 2012;2:22.
35. ClinicalTrials.gov website. http://www.clinicaltrials.gov/ct2/show/NCT01271803?term=GDC-0973&cond=%22Melanoma%22&rank=2. Accessed February 25, 2013.
36. ClinicalTrials.gov website. http://www.clinicaltrials.gov/ct2/show/NCT01689519?term=GDC-0973&cond=%22Melanoma%22&rank=1. Accessed February 25, 2013.
37. Jakob JA, Bassett RL Jr, Ng CS, et al. NRAS mutation status is an independent prognostic factor in metastatic melanoma. *Cancer.* 2012;118
(16):4014-4023.
38. Winski S, Anderson D, Bouhana K, et al. MEK162 (ARRY-162), a novel MEK ½ inhibitor, inhibits tumor growth regardless of KRas/Raf pathway mutations. Proceedings of the 22nd EORTC-NCI-AACR symposium on Molecular Targets and Cancer Therapeutics; Berlin, Germany; Nov 16-19, 2010.
39. ClinicalTrials.gov website. http://www.clinicaltrials.gov/ct2/show/NCT01320085?term=MEK162&cond=%22Melanoma%22&rank=3. Accessed March 4, 2013.
40. ClinicalTrials.gov website. http://www.clinicaltrials.gov/ct2/show/NCT01781572?term=MEK162&cond=%22Melanoma%22&rank=2. Accessed March 4, 2013.
41. ClinicalTrials.gov website. http://www.clinicaltrials.gov/ct2/show/NCT01763164?term=MEK162&cond=%22Melanoma%22&rank=1. Accessed March 4, 2013.
42. Jang S, Atkins MB. Which drug, and when, for patients with BRAF-mutant melanoma? *Lancet Oncol.* 2013;14(2):e60-e69.
43. Gilmartin AG, Bleam MR, Groy A, et al. GSK1120212 (JTP-74057) is an inhibitor of MEK activity and activation with favorable pharmacokinetic properties for sustained in vivo pathway inhibition. *Clin Cancer Res.* 2011;17(5):989-1000.
44. Frederick DT, Adriano P, Cogdill AP, et al. BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma [published online January 10, 2013]. *Clin Cancer Res.*
45. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med.* 2013;367(2):107-114.
46. Kim KB, Kefford R, Pavlick AC, et al. Phase II study of the MEK1/MEK2 inhibitor trametinib in patients with metastatic BRAF-mutant cutaneous melanoma previously treated with or without a BRAF inhibitor. *J Clin Oncol.* 2013;31(4):482-489.
47. ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/results?term=Trametinib&cond=%22Melanoma%22. Accessed February 22, 2013.
48. Zitvogel L, Kroemer G. Targeting PD-1/PD-L1 interactions for cancer immunotherapy. *Oncoimmunology*. 2012;1(8):1223-1225.
49. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med.* 2012;366(26):2455-2465.
50. Ribas A, Hauschild A, Kefford R, et al. Phase III, open-label, randomized, comparative study of tremelimumab (CP-675,206) and chemotherapy (temozolomide [TMZ] or dacarbazine [DTIC]) in patients with advanced melanoma. *J Clin Oncol.* 26:2008 (May 20 suppl; abstr LBA9011).
51. Falchook GS, Long GV, Kurzrock R, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumors: a phase 1 dose escalation trial. *Lancet.* 2012;379(9829):1893-1901.
52. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2012;13(11):1087-1095.
53. Hauschild A, Grab J, Demidov L, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomized control trial. *Lancet.* 2012;380(9839):358-365.
54. ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/show/NCT01153763?term=Dabrafenib&cond=%22Melanoma%22&rank=9. Accessed February 22, 2013.
55. ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/show/NCT01266967?term=Dabrafenib&cond=%22Melanoma%22&rank=7. Accessed February, 2013.
56. ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/results?term=Dabrafenib&cond=%22Melanoma%22. Accessed February 22, 2013.
57. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med.* 2012;366(26):2443-2454.
58. ClinicalTrials.gov website. http://www.clinicaltrials.gov/ct2/results?term=BMS-936559+melanoma&Search=Search. Accessed March 4, 2013.
59. ClinicalTrials.gov website. http://www.clinicaltrials.gov/ct2/results?term=nivolumab+melanoma&Search=Search. Accessed March 4, 2013.
60. Bedikian AY, Millward M, Pehamberger H. Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the oblimersen melanoma study group. *J Clin Oncol.* 2006;24(29):4738-4745.
61. Jansen B, Schalagbauer-Wald H, Brown BD, et al. Bcl-2 antisense therapy chemosensitizes human melanoma in SCID mice. *Nat Med.* 1998;4(2):232-234.
62. Klasa RJ, Gillum AM, Klem RE, et al. Oblimersen Bcl-2 antisense: facilitating apoptosis in anticancer treatment. *Antisense Nucleic Acid Drug Dev.* 2002;12(3):193-213.
63. Ott PA, Chang J, Madden K, et al. Oblimersen in combination with temozolomide and albumin-bound paclitaxel in patients with advanced melanoma: a phase I trial. *Cancer Chemother Pharmacol.* 2013;71(1):183-191.
64. Chanan-Khan AA, Niesvizky R, Hohl RJ, et al. Phase III randomised study of dexamethasone with or without oblimersen sodium for patients with advanced multiple myeloma. *Leuk Lymphoma.* 2009;50(4):559-565.
65. ClinicalTrials.gov website. http://www.clinicaltrials.gov/ct2/show/NCT00409383?term=oblimersen&cond=%22Melanoma%22&rank=3. Accessed March 3, 2013.

Value-Based Contracting for Pharmaceuticals: Getting Ready for Prime Time?

Stanton R. Mehr

The full-court press toward comparative-effectiveness research and results reporting has compelled health plans and insurers to sharpen their focus on incorporating this information into coverage decision making. Managed care executives have long complained that too few evidence-based data of this type are available to improve coverage decisions. If the evidence were available and payers were ready to incorporate it, widespread development of value-based formularies might result.

Any pharmaceutical manufacturer whose small-molecule drug is the third or fourth product of a category to reach the market faces its own value-based quandary: How can it prove the value proposition of its agent in the face of heavy competition? Drug rebates and discounts can provide access to a plan's membership, but this does not truly address the economic value of a drug. The question is even more difficult (and scrutinized) in the case of expensive biologic medications. A survey published in 2012 demonstrated that managed care executives are not satisfied with the current approach of contracting and discounts to obtaining formulary access.[1] Only 4% indicated that they were "very satisfied" with this form of contracting.

One innovation that has yet to become mainstream involves manufacturers offering to back their product's performance by taking some of the risk. This does not necessarily mean a "money-back guarantee," but it certainly could. This is in stark contrast to the present situation, where the manufacturer's "risk" has been defined by the difficulty in successfully navigating the drug development process from preclinical studies through US Food and Drug Administration (FDA) approval, and subsequently, the risk in marketing the drug successfully to payers. This risk must not be minimized—according to past reports from the Tufts Center for the Study of Drug Development (www.csdd.tufts.edu), the cost to develop biotechnology drugs was approximately $1.2 billion in 2006. In addition, the pharmaceutical industry spends hundreds of millions of dollars on marketing efforts to increase awareness and focus on their products' benefits.

Today's price-volume agreements or patient-access initiatives (where patients would be given access to a drug at reduced cost to try to prove value to payers, in the hope of landing preferred formulary positioning) are a form of "value-based contracting,"[2] but if outcomes are what the payers are after, these contracts are low on the evolutionary scale. "Outcomes-based contracting" represents the next evolution, encompassing risk-based agreements with performance guarantees or payment scales for attaining not utilization or market share benchmarks, but clinical status improvement or prevention of adverse events. This is truly value-based contracting. It boils down to the following: if the drug doesn't provide the outcome that is expected, the manufacturer would be at risk in some way—reimbursement would be discounted or possibly even free, or the manufacturer would bear the cost of complications suffered by the patient. It may make it more palatable for payers to cover an expensive agent, and gain credibility for the maker of a specialty drug.

Robert Kritzler, MD

If the pharmaceutical companies will need to eventually move away from volume-based sales, it would be reasonable to expect "the industry to shift into a world in which outcomes-based contracting will be the standard reimbursement methodology," according to one pharmaceutical executive.[1] Yet, this concept has not spread to date. Pay for performance has been utilized for provider reimbursement for a decade.[3] Why not apply this concept to pharmaceuticals? Assuming one does not run afoul of federal anti-kickback statutes, and the remuneration, discounts, or incremental reimbursement resulting from an outcomes-based contract that can be coordinated under an accepted safe harbor,[4] then one can explore some of the outcomes-based pharmaceutical contracting options being discussed today.

Specialty Pharmaceuticals Shine a Light on the Issue

The costs associated with specialty pharmaceuticals continue to concern payers and represent a difficult challenge for the years ahead. Specialty pharmaceuticals today account for 80% of the total drug spend in the medical benefit, and 8 of the top 10 drug categories in 2014 are forecast to be specialty drugs.[5] In the future, specialty utilization is expected to grow rapidly, owing to new drug introductions and rising numbers of patients with chronic diseases for which specialty drugs may be indicated. Robert Kritzler, MD, deputy chief medical officer, Johns Hopkins HealthCare, Glen Burnie, Maryland, believes that "with the rising cost of specialty pharmaceuticals, especially those with variable outcomes based on patient selection, there will need to be a different way of contracting."

Payers are not yet convinced of the value proposition behind these products. They are actively seeking reassurances that an agent that may cost $10,000 for each month of therapy is money well spent. This is partly behind the push for companion diagnostics, to help determine those patients who may optimally benefit from the use of specific specialty drugs. It is also responsible for the interest in performance guarantees and other ways to link a drug's costs to its actual outcome in the patient.

Gerald Clor, MBA

"The pharmaceutical and biotech industries have done a bad job of clearly stating the value equation and life-saving value of their products," asserted Gerald Clor, MBA, of Clor Training & Consulting, LLC, Bethlehem Township, Pennsylvania. "Health plans do not want to be seen as 'being too close' to such a negative industry—especially when it is a business proposition."

Clor continued, "This potential to help patients, improve care, and lower costs is partially lost owing to the 'politics' of the current state of affairs within the pharmaceutical industry. Too many big pharmaceutical companies have been caught behaving badly and brought into the public eye. How then can a health plan expect to partner with them? So politics and public sentiment trump good medicine in this case."

Myeloma Drug Pioneers the Concept

In 2007, the prototype value-based or performance-based contract for a drug was introduced in the United Kingdom by Johnson & Johnson.[6] The National Institute for Clinical Excellence (NICE) had deemed its product Velcade provided too little value for the cost to recommend coverage by the National Health Service. The company, worried about being locked out of the British market, offered a radical contract: The use of the drug must achieve a 50% reduction in serum paraprotein (M-protein) levels by the fourth cycle of therapy or the manufacturer would reimburse the National Health Service the full cost of the drug. Technically, this compensation was most commonly made in the form of additional free Velcade.[2] The decision makers at NICE took them up on their offer.

The first value-based pharmaceutical contracts in the United States were seen in 2009. One well-publicized contract was between Cigna and Merck for the diabetes products sitagliptin and sitagliptin/metformin. Merck provided discounts if Cigna members with type 2 diabetes mellitus lowered their blood sugar levels, and also provided for additional discounts if people who were prescribed Merck's drugs took their medications according to their physicians' instructions. In return, Cigna placed the agents on a low copayment tier, in the hopes of optimizing adherence to the

Table. Perception of Value

	Biopharmaceutical company	Biopharmaceutical services provider	Generic pharmaceutical company	Health insurance company	Government payer	Regulatory agency
Degree of improved efficacy over existing products	49%	28%	34%	27%	19%	26%
Total patient outcomes	55%	58%	27%	32%	26%	23%
Whether it addresses an unmet medical need	36%	31%	34%	21%	29%	24%
Potential number of patients who could use the drug	14%	14%	56%	31%	29%	19%
Costs compared with competing products	29%	36%	32%	26%	23%	25%
Improved longevity of patient	17%	11%	17%	29%	492%	25%
Improved quality of life of patient	26%	28%	34%	58%	52%	70%

Source: Economist Intelligence Unit survey, September 2011
Responses to the question, "In the next 3 years, which, if any, of these attributes will become significantly more important in your assessment of the value of a new drug?" Adapted with permission from Kielstra P. Reinventing biopharma: strategies for an evolving marketplace–the value challenge. The Economist Intelligence Unit. April 25, 2012. http://www.slideshare.net/Management-Thinking/the-value-challenge-reinventing-biopharma-strategies-for-an-evolving-marketplace. Accessed February 19, 2013.

medication.[6] According to a Cigna press release, "The results demonstrated improved blood sugar levels of more than 5% for those continuously enrolled in the program, regardless of which diabetes drug they were taking. There was also a 4.5% increase in blood sugar lab testing during the period."[7]

Also in 2009, Health Alliance Plan contracted with Procter & Gamble and sanofi-aventis on the osteoporosis drug Actonel (risedronate). In this deal, the manufacturers agreed to reimburse Health Alliance Plan for the costs of treating nonspinal, osteoporosis-related fractures in eligible postmenopausal women who were using the product, up to a predefined amount, which greatly limited their financial risk. This gamble worked well, as the effectiveness of the osteoporosis drugs in general were heavily questioned at this time, and the arrangement ensured health plan members had access to risedronate. Nine months after starting the program, the manufacturers found that they had paid far less (79% less) than the predefined limit established in the contract. In addition, the data gained corroborated Procter & Gamble's original clinical trial data for risedronate's efficacy in preventing nonspinal fractures.[8] Furthermore, it may have delayed the plan's generic substitution for risedronate, as well as kept it in preferred position relative to the newer branded product Boniva (ibandronate).

In general, non-US payers are interested in seeking alternative methods of payment for pharmaceuticals. Although NICE is currently utilizing cost-effectiveness thresholds in making coverage recommendations, it is seeking to revamp its decision making as it applies to any new drug by 2014, and include other factors as well, such as unmet need, the burden of illness, degree of innovation associated with a new medicine, and additional societal benefits gained with the new medicine. This value-based pricing system will supplant the existing system used by the National Health Service when evaluating all new medications.[9]

Australia, Germany, and Italy have all undertaken several initiatives aimed at increasing the number of outcomes-based pharmaceutical contracts.[1] The Australian drug pricing authority has at least 90 contracts of this type on the books. There is no lacking for motivation among payers worldwide. It is only a matter of time before US payers are greater players in this area.

Hurdles to Overcome in Outcomes-Based Pharmaceutical Contracting

If 1 word characterizes the nature of outcomes-based contracting for pharmaceutical drugs, it is "complexity." Gerald Clor believes that multidrug therapy, promoted by many clinical guidelines, muddies the waters quite a bit. "It becomes very difficult to measure the impact of clinical improvement when there is more than 1 single aspect to that improvement," he said. "Few companies will want to enter into a risk-shared contract if the measure of success goes past the drug monotherapy."

Just coming to agreement on which outcomes measures are actually of importance is a notable obstacle. For example, according to one survey, payers focus on measures of longevity and quality of life, but pharmaceutical manufacturers are focused on specific units of clinical efficacy or the "cost-benefit implications of a new drug for overall treatment." Furthermore, healthcare providers and patients may point to other preferred outcomes measures.[9]

Adding to this measure of complexity is the desire to move toward new payment methods. "If a 'bundled' or 'global' payment is used, and the goal is to lower the total cost of care," Clor wondered, "how do I measure my (pharmaceutical) impact on that cost parameter? This complication adds too many variables and components that the contract (or the drug company) cannot control."

These challenges are difficult to overcome from a pharmaceutical manufacturer's perspective. From the health plan perspective, the complexity of these arrangements is no less an issue. Dr Kritzler of Johns Hopkins Health Care explained, "Many plans, including our own, have considered some sort of value-based contracting based on final outcome. Areas that many of us have considered are in the oncology, neurology, and the autoimmune space," he commented, "but plans are having a rough time implementing this, as the details are extraordinarily complex."

Not only are the details to implementation complex, but the administration of these types of contracts can be barriers to payers. Assume that they would need a tracking mechanism for particular patients' clinical status over time. In some cases, they would save less money from the outcomes-based contract than it would cost to launch and manage the patient tracking system needed to analyze the intervention's effects.

However, Dr Kritzler believes that once the ball begins rolling, it will be hard to stop. "As soon as a few of these arrangements gain traction, it is likely that this type of contracting will take off," he said.

Oncology-Specific Questions

The idea of outcomes-based contracting for oncology products adds a new level of complexity to an already challenging issue. How to measure outcomes becomes not only a question about the value of overall survival versus progression-free survival or complete response versus clinical response as a clinical or patient-related outcome, but consider the next stage of discussion: Would the terms of the outcomes-based oncology contract change for patients diagnosed at a different stage of cancer? For example, should the successful outcomes of a drug given in patients with stage III tumors be judged differently from the outcomes of a drug given in patients with stage I or II disease? These permutations can boggle the mind. In addition, how might a contract define objective result reporting?

With these questions in mind, it should not be surprising to see initial outcomes- or value-based contracting efforts focused on other diseases. Although oncology is an area that may optimally benefit from this approach—many primary drug treatments qualify as specialty pharmaceuticals—it may not be practical for many cancers.

Still, Johnson & Johnson successfully implemented and administered its Velcade contract with NICE, so there is some experience to build upon. In this example, M-protein may not be a good outcomes indicator of survival.[2] Furthermore, up to 15% of all patients do not have measureable M-protein levels.[2]

A value-based approach might help advance an approach that emphasizes biomarker testing before treatment, to help identify who would be most likely to benefit. Additionally, such contracting could be an incentive for manufacturers to engage in greater efforts to educate providers as to who might be the most appropriate subpopulations of patients for these expensive agents.

The Pace of Change Is Slow

The industry has just begun to consider what payers mean when they say they want more value for the money they spend. A survey by a unit of *The Economist* found that the biopharmaceutical industry is a harsh critic of the progress

made to date (**Figure**).[10] The survey report specifies that "More than one-half of respondents overall (55%) say that the sector is adjusting well to increasing demands for proof of value, but only 36% from traditional biopharmaceutical companies agree."[10] Furthermore, just over half (56%) believe that "The industry will introduce products with demonstrably more value than existing offerings in the next 3 years. Worse still, only 39% believe that the industry is more than just somewhat effective at creating such products." Not insignificantly, the survey respondents didn't believe that the industry does a good job of proving value, even when their products may be of real value. Only 25% of payers and government policy makers interviewed expressed a level of confidence about claims of value made by the industry.[10]

Based on PriceWaterhouseCoopers' analysis, it is imperative that payers and pharmaceutical manufacturers hold numerous discussions and hold them early in the contracting process "to determine what is of value to each stakeholder."[1] This may be augmented by developing formal, well-defined, consensus-driven value metrics, and by obtaining a consensus on a "common set of principles, policies, and technical methods for the data collection program." Without this extremely high level of agreement on what constitutes an outcome of value to both payer and manufacturer, the vast effort to develop outcomes-based pharmaceutical contracts (for any disease category) will be destined to fail.

Funding Source: None.

Author Disclosure: Mr Mehr reports receiving payment for involvement in the preparation of this article.

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

References

1. Unleashing value: the changing payment landscape for US pharmaceutical manufacturers. PriceWaterhouseCoopers Health Research Institute. http://www.pwc.com/us/en/health-industries/publications/pharma-reimbursement-value.jhtml. Published May 2012. Accessed February 1, 2013.

2. Adamski J, Godman B, Ofierska-Sujkowska G, et al. Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. *BMC Health Serv Res.* 2010;10:153-169.

3. 2011 annual report. Integrated Healthcare Association, Oakland, California. www.iha.org/pdfs_documents/resource_library/IHA_AnnualReport_2011_Final.pdf. Accessed January 25, 2013.

4. Lutes ME, Gottlieb DG. Managing regulatory risk in value-based contracting. Presented at Value-Based Contracting and Risk-Sharing Agreements, Sponsored by CBI. Philadelphia, PA: January 30-31, 2013.

5. 2011 care insights: changing rules changing roles. Scottsdale, AZ: CVS Caremark; 2012.

6. Pollack A. Drug deals tie prices to how well patients do. *New York Times*, April 23, 2009. http://www.nytimes.com/2009/04/23/business/23cigna.html?_r=0. Accessed February 2, 2013.

7. Cigna and Merck help customers better manage diabetes (press release). Cigna, October 28, 2010. http://newsroom.cigna.com/article_display.cfm?article_id=126. Accessed February 14, 2012.

8. Issue brief: value-based pricing for pharmaceuticals: implications of the shift from volume to value. Deloitte Center for Health Solutions; 2012. http://deloitte.wsj.com/cfo/files/2012/09/ValueBasedPricingPharma.pdf. Accessed February 1, 2013.

9. Faden RR, Chalkidou K. Determining the value of medications—the evolving British experience. *N Engl J Med.* 2011;364:1289-1291.

10. Kielstra P. Reinventing biopharma: strategies for an evolving marketplace—the value challenge. The Economist Intelligence Unit. April 25, 2012. http://www.slideshare.net/Management-Thinking/the-value-challenge-reinventing-biopharma-strategies-for-an-evolving-marketplace. Accessed February 19, 2013.

Payer Perspective

Outcomes-Based Contracting for Pharmaceuticals: A Health Plan Perspective

Jeffery D. Dunn, PharmD, MBA

Outcomes-based contracting for pharmaceuticals has been discussed for years as an incentive to offer preferred formulary positioning for certain drugs and to lower costs. Drug categories and their associated outcomes have included diabetes agents and reductions in hemoglobin A1C; bisphosphonates and decreased fracture rates; statins and cholesterol lowering; and even guarantees against dose escalation in specialty categories like rheumatoid arthritis and psoriasis.

However, true outcomes-based contracting is elusive. Many healthcare plans are incapable of capturing, measuring, and reporting the data elements necessary to comply with the contract terms. Even integrated plans lack the information technology to adequately marry medical claims with pharmacy data. Furthermore, most contracts would require plans to manage down to the individual member level rather than use high-level aggregate data that are typically required for rebates.

It is also often difficult to identify and agree on what outcomes will be measured. It can be done with objective measures such as low-density lipoprotein and hemoglobin A1C levels, but when exploring more intriguing disease states, such as multiple sclerosis, rheumatoid arthritis, and oncology, the outcomes are often subjective. For example, a plan cannot be expected to define what is progression-free survival in a patient with metastatic prostate cancer or what is a clinically significant relapse in multiple sclerosis.

Plans also often find the investment in maintaining and complying with the contracts not worth the return warranted by the effort expended, partly because the pharmaceutical manufacturers have never gone truly at risk. Using a previously mentioned example, a bisphosphonate contract was touted as paying for the cost of a fracture if patients were compliant with the drug therapy. However, there was a cap on the exposure to the manufacturer—a maximum payment was set at a percentage of plan spend on the drug. This was substantially less than the total cost of any 1 fracture. For the diabetes and statin examples, the manufacturers offered a few extra percentage rebate points if a plan's population met certain A1C or lipid goals. Often this results in a few thousand dollars in incremental rebates, which needs to be weighed against the effort required to code and measure the input data (not even considering the requests to stratify risk, which can't be accomplished through claims databases). There is also the issue of how a plan addresses, and invests in, the education or incentives necessary to change both prescriber and member behavior to improve the respective lab values or outcome measures. These measures and activities would often have to be above and beyond what is occurring for quality measurements such as HEDIS or Medicare Star ratings.

Despite the poor history of these types of contracts, they will continue to be explored, owing to the shift toward specialty drug management. It will be more feasible to implement outcome-based contracts in these categories, because the sample size is much smaller and can be more easily measured at a member level, and the cost of the drugs is significantly higher, making the return to the managed care plan potentially much higher.

In conclusion, most plans cannot comply with outcomes-based contracts. This is not for lack of desire but rather operational or philosophical shortcomings. However, we need to figure out a way for all stakeholders to share risk as we move toward more niche specialty drugs, new models of healthcare delivery, and payment reform. Pharmaceutical companies should have an active role in backing up the efficacy, or lack thereof, of expensive medications that currently are paid for by plans and members. The government, FDA, or other body may play a role in requiring manufacturers to provide a value proposition for all medications similar to that played by the National Institute for Clinical Effectiveness in the United Kingdom. All stakeholders (plan, provider, member, manufacturer, and government) must have a role in delivering value in medications and delivering cost-effective healthcare.

Dr Dunn is formulary and contract manager for SelectHealth in Salt Lake City, UT.

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

THE POWER OF SECOND-GENERATION PROTEASOME INHIBITION TAKES FLIGHT

Important Safety Information

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

Kyprolis™ (carfilzomib) for Injection is engineered for selective inhibition[1]

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

ADVERSE REACTIONS

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

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

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

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

Kyprolis™ (carfilzomib) for Injection

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

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

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

ADVERSE REACTIONS

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

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

USE IN SPECIFIC POPULATIONS

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

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

ONYX PHARMACEUTICALS

Kyprolis™ (carfilzomib) for Injection

KYPROLIS™ (carfilzomib) for Injection

Brief Summary of Prescribing Information. Please see the KYPROLIS package insert for full prescribing information.

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

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

Table 1: KYPROLIS Dosage Regimen for Patients with Multiple Myeloma

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

[a]If previous cycle dosage is tolerated.

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

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

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

(continued)

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

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

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

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

Table 3: Stability of Reconstituted KYPROLIS

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

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

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

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

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

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

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

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

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

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

[b]One event was Grade 5 severity.

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

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

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

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

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

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

ONYX PHARMACEUTICALS

Manufactured for: Onyx Pharmaceuticals, Inc., 249 East Grand Avenue, South San Francisco, CA 94080

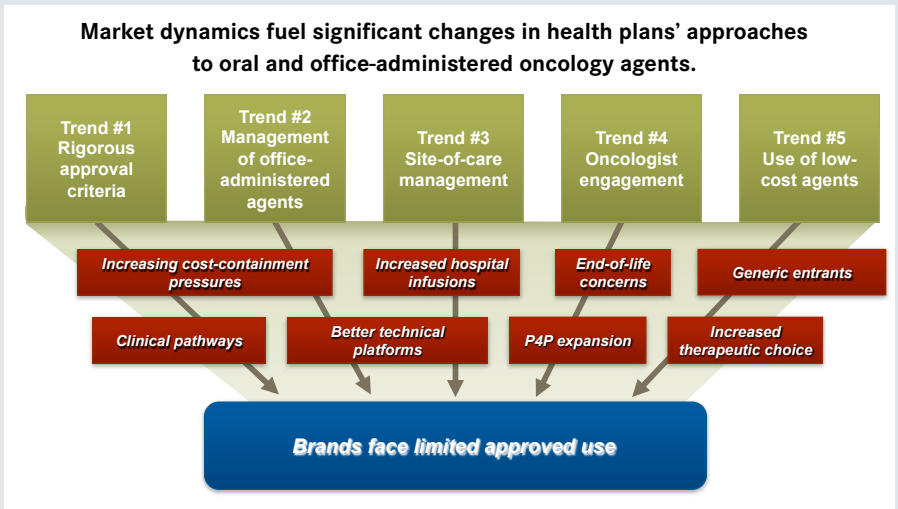
U.S. Patent Numbers: 7,232,818; 7,417,042; 7,491,704; 7,737,112 05-1088-00

THE AMERICAN JOURNAL OF MANAGED CARE®

Story Jumper

(continued from cover)

Figure 1. Emerging Plan Access Approaches in Oncology



P4P indicates pay for performance.

include both market factors and new payer capabilities.

External, Internal Factors

The way health plans make decisions on oncology agents is changing in part because of their success containing costs in other complex drug categories comprising both self-injected and office-administered biologics, such as autoimmune and multiple sclerosis (MS) agents. Plans also have better information technology (IT) with expanded capabilities in data analysis, so they can identify inappropriate use and refine drug reimbursement. These improved capabilities—combined with the expanded choices afforded by new drug approvals and generic options, as well as a robust pipeline—are driving plans' interest in using more management tactics.

Likely Short-Term Steps

With their focus squarely on oncology agents, payers will take several management actions in the short term. For instance, newly approved oral oncolytics will face high cost-sharing requirements. Many plans will change their benefit designs—by adding more tiers or raising copay levels, for example—to increase cost sharing. Half of plans already require members to pay additional fees for office-administered drugs, and more plans will follow suit.

Payers will also roll out clinical pathways that cover more tumor types and more oncologists in their networks. During this expansion, plans will rely on compendia guidelines from the National Comprehensive Cancer Network and other organizations to guide pathways. If successful, these pilots will help create the foundation for greater control of access. Health Strategies Group expects that after rolling out the additional pathways, plans will start narrowing pathway choice to specific first-line agents beginning in 2015.

While these strategies are suited for the short term, they do not address payers' goals over the long haul. Our research suggests that shifting management priorities are likely to generate 5 trends during the next 5 years (Figure 1).

Pullquote here and here. Pullquote here and here. Pullquote here and here. Pullquote here and here.

—Name
Title
Location or name of place

Trend #1: Rigorous Approval Criteria

Plans say they will narrow prior authorization (PA) approval criteria to restrict use of oncology agents, particularly high-cost agents lacking substantial survival improvements. As they commonly do today, health plans will use PAs to ensure alignment with labeling and compendia (Figure 2). In addition, 60% of plans expect to influence treatment order by requiring trials of specific first- and second-line agents. As new therapeutic choices emerge to treat certain tumor types, such as metastatic breast cancer and prostate cancer, we expect more plans to adopt a similar "lines of therapy" strategy. In addition, more plans will manage therapy duration by not only prospectively confirming treatment plans but also requiring reauthorization for extended use of a product.

Despite these efforts, plans recognize that PAs have a limited role and that pathways are a better long-term strategy to ensure appropriate use. As plans roll out clinical pathways, they will likely remove PA requirements.

To encourage provider adherence to the new pathways, plans will likely ask oncologists for their input and provide technology that helps integrate the pathways into their process. In addition, plans will likely provide financial incentives to oncologists to encourage adherence.

Trend #2: Management of Office-Administered Agents

Office-administered agents will face more access barriers. In the past 18 months, many plans rolled out changes to their infrastructure to improve management of these drugs. One of the newest changes is claims adjudication by National Drug Code (NDC) data. Widespread plan requirements to collect NDC data in claims submissions by 2014 will improve plans' ability to enforce use of low-cost agents. With the data specificity provided by NDC codes, plans can set different reimbursement amounts for generic and branded options, reducing physicians' incentive to use high-priced choices.

Oncologists should expect even greater communication with payers around alignment as more practices implement electronic medical records (EMRs). Automatic payer precertification through EMRs will save time and reduce financial risks for practices. Plans will also benefit from greater alignment as oncologists are able to view pathways and PA criteria in "real time." This technology will provide plans with more opportunities to build tools that can help them manage office-administered agents.

Trend #3: Site-of-Care Management

Moving forward, plans will take steps to influence site of care and move administration of office-administered oncology agents away from hospitals. Their goal will be to drive patients to the most cost-effective setting, which may be a specialty pharmacy manager. However, plans are somewhat limited in how they can drive the local market dynamics that determine where patients receive these agents. Of late, these dynamics include more hospitals buying up oncology practices, a trend that has driven steady increases in hospital outpatient infusions in some markets. In addition, diminishing profit margins on drugs have prompted some oncology groups to refer patients to hospital outpatient departments for infusions. Accountable care organization growth may accelerate this trend.

For now, the best tool for plans is to ratchet down hospital reimbursement, which 46% of plans will try in 2014 (Figure 3). In addition, many plans will pilot reimbursement models, including episodic payments that encourage providers to select low-cost administration locations. Integrated health plans with strong relations with oncology groups will likely lead this effort. Plans may

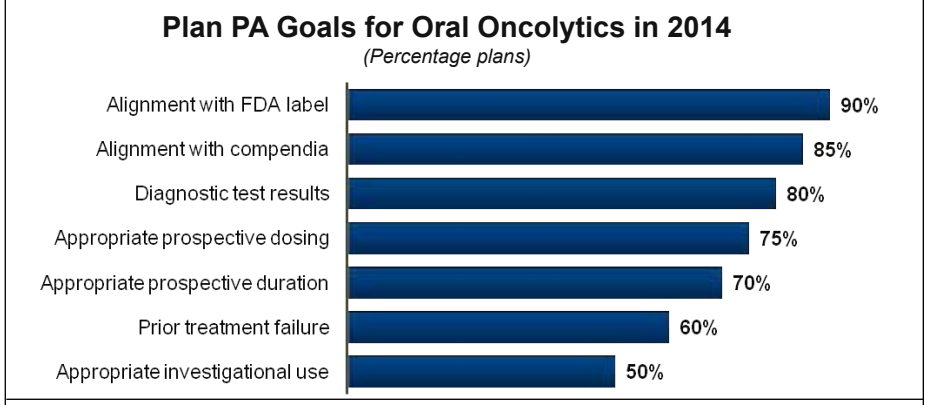
Figure 2. Prior Authorization (PA) Goals for Oral Oncolytics in 2014

Plans will narrow PA approval criteria to restrict use of high-cost agents lacking substantial survival improvements.

Initial approval criteria will prospectively confirm dosing, duration.

More plans will require reauthorization for extended use.

Plans will remove PA requirements when pathways roll out.



FDA indicates US Food and Drug Administration.

Figure 3. Anticipated Plan Tactics to Reduce Hospital Administration in 2014

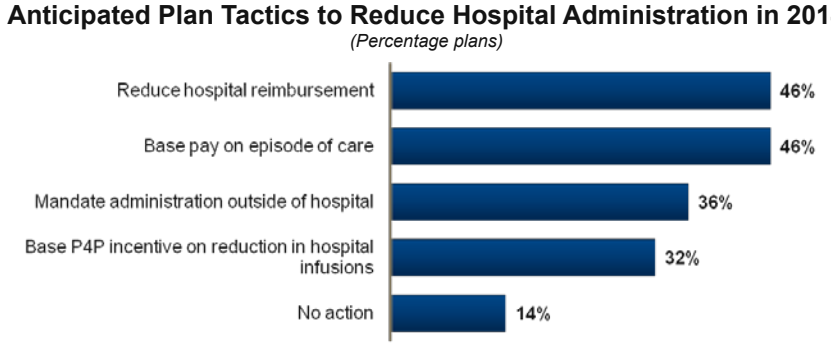
Plans may take steps to influence site of care.

Site-of-care challenges vary by local market area.

Some plans may pilot episodic payment models.

Plans will consider more fundamental network design changes.

"We want to make sure that what we pay for is in the most cost-effective setting, whether it's the physician's office or a freestanding infusion center, but not the outpatient hospital." – *Regional Independent Medical*



P4P indicates pay for performance.

also consider more fundamental network design changes, such as only offering "preferred" or "in-network" status to hospitals with reasonable infusion charges.

Trend #4: Oncologist Engagement

Recognizing that oncologists are key partners in their efforts to provide better value and higher-quality care, plans will introduce new financial incentives to influence provider decisions. These will include oncologist-specific pay-for-performance (P4P) programs, which will reward oncologists for cost-of-care reductions, quality improvements, increased generic prescribing, reduced hospital infusions, and other goals. Plans are in a better position than ever before to implement P4P with oncologists—building on their experience designing P4P for primary care providers, plans can refine their approaches for the unique challenges of oncologists. These challenges include the availability of new generics as well as the wide variation in prescribing in oncology.

Plans have yet to develop an effective solution for managing the high costs of care at the end of life (EOL). Given the sensitive nature of this topic, plans aren't likely to deny therapy to patients with advanced cancer. For their part, oncologists are often reluctant to have EOL discussions with their patients. One possible solution for plans would be to utilize case managers and social workers to initiate advance care planning, although they would need to be careful not to overstep their bounds. Another possibility is for plans to increase payments to oncologists for holding counseling sessions and include a counseling metric in their P4P programs, thereby paying oncologists for discussing the options with their patients.

Trend #5: Use of Low-Cost Agents

As part of their long-term management strategy, plans will take more aggressive steps to maximize oral generic use. Multisource availability of Gleevec (imatinib), likely in 2014, will provide a significant cost-saving opportunity. Almost two-thirds of plans intend to reimburse Gleevec on a higher copay tier, and over one-third say they will require a trial of imatinib prior to covering Sprycel (dasatinib) or Tasigna (nilotinib) (**Figure 4**). These intended moves demonstrate payers' increasing willingness to influence therapy order—fewer plans were interested in taking such actions as recently as 2010.

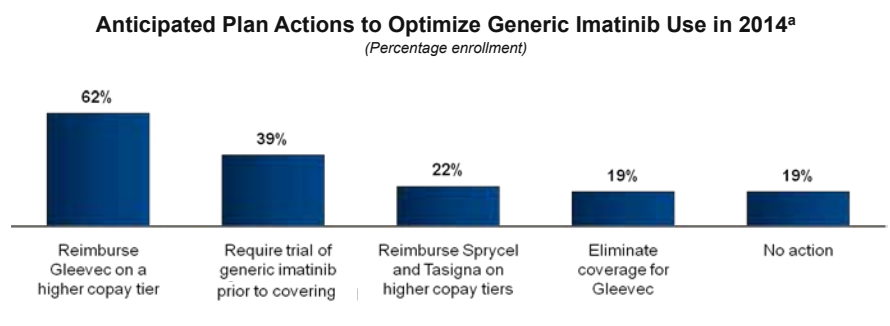
Recognizing that oncologists are key partners in their efforts to provide better value and higher-quality care, plans will introduce new financial incentives to influence provider decisions.

Figure 4. Anticipated Plan Actions to Optimize Generic Imatinib Use in 2014

Plans will take steps to maximize oral generic use.

When the price is 50% less, most plans (up from 43% in 2011) will require imatinib use prior to covering competitive brands Sprycel and Tasigna.

Plans will promote expansion of generic trials by embedding recommendations in clinical pathways or PA criteria.



Plans will also take steps to increase use of generic alternatives for office-administered agents in the next few years, primarily by embedding recommendations in clinical pathways or PA criteria. But encouraging use of these lower-cost infused agents is a little trickier for plans. Coding and current fee schedules need to be refined to neutralize profit incentives associated with brands and encourage generic use.

More Access Barriers Down the Road

Payer adoption of these emerging trends will vary greatly. In the short term, health plans will likely focus on improving patient and physician support, rather than implementing penalties and coverage denials. Over time payers will be more interested in advanced management strategies that require collaboration with providers to ensure appropriate use. **EBO**

Acknowledgments

All figures and statistics in this article are based on the 2012 findings of Health Strategies Group's *Managed Care Complete* research series, which reports on 10 categories, including oral oncolytics and office-administered oncology agents. *Managed Care Complete* provides future-oriented, strategic insights on the decisions that all relevant managed care customers and business lines make that affect brand access. Health Strategies Group offers syndicated research and client-private consulting, which focus on understanding the pharmaceutical and biotech industry's key customers and influencers.

Author Affiliation: From Health Strategies Group, Redwood City, CA.

Funding Source: None.

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

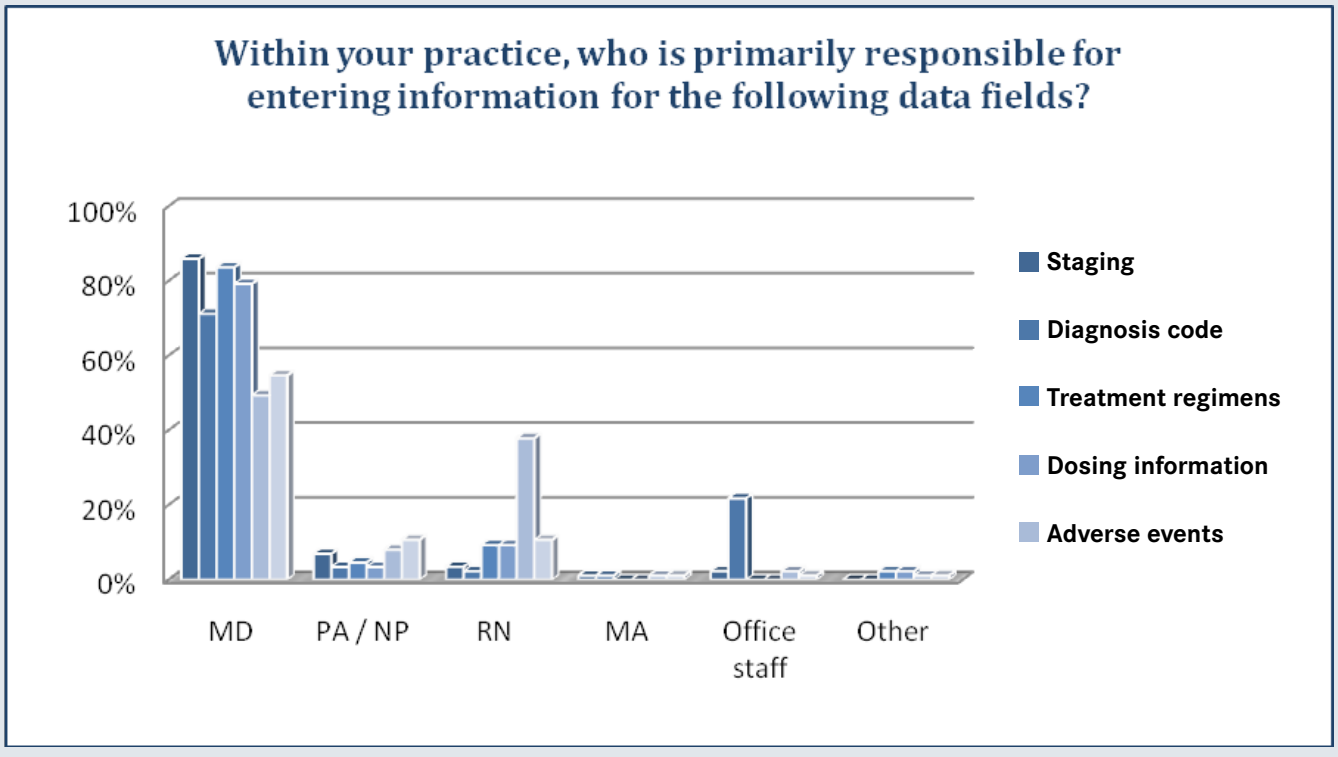
Authorship Information: Concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; administrative, technical, or logistic support; and supervision.

Author correspondence to: Susan Weber, Research Director, Health. Strategies Group, 303 Twin Dolphin Dr, Ste 600, Redwood City, CA 94065. E-mail: sweber@healthstrategies.com.

THE AMERICAN JOURNAL OF MANAGED CARE

Story Jumper
(continued from ##)

Figure 1. From 87 Oncology Practices Using an EMR and Surveyed in 2009



critical to those of us who have a cancer diagnosis in our family or in our future—and that is just about everyone. Providers must participate in the move to active measurement of clinical variables or become obsolete. They must also integrate reporting and measurement of important process measures into routine clinical management. Payers have a critical role in promoting this technology adoption. They are positioned to promote payment methodologies that support and reward clinical measurement. Without such support, innovative practices suffer economically as they push toward rational care. We all should expect basic quality process measures that are indicative of good clinical management of cancer care for our families and ourselves. Successful payers and providers will encourage patients to seek care where these quality indicators are available and exemplary.

The presence of specific, essential clinical information as structured data in the clinical database is necessary for oncology care management.

Discussion

Three visions of performance metrics in oncology were presented at the Cancer Center Business Summit held October 11-12, 2013, in Fort Worth, Texas. The theme of the conference was transitioning to value-based oncology and most of the program content, including the full program that is summarized in this article, is available online.[2] While the 3 perspectives are different, there were consistent themes throughout. All speakers endorsed the use of available data, keeping metrics simple, delivering measurements to the care providers who can affect the numerator, and showing these providers how they compare with peers. The speakers all understand that current payment methodology does not support process optimization, yet view that as a transitional barrier that will not persist.

I presented the 3 criteria that are generally accepted for choosing clinical performance measures.[3] To be successful, measures must be important, scientifically sound, and feasible. Importance is measured by the relevance of the measure to patients and providers and the promise that being measured offers for improvement. To be scientifically sound, there must be substantial, explicit evidence with validity, reliability, and sufficient specificity to patient factors to be clinically useful. Feasibility requires an explicit definition of the numerator and denominator needed for the measure from data that are available at low cost and with low administrative burden. Today the fact is that payment drives process measurement and most systematic data are about billing, not about medical care. The EHR incentive program, coupled with many providers and payers seeking a departure from fee for service, are factors driving oncology data feasibility toward important, scientifically sound measurements.

The presence of specific, essential clinical information as structured data in the clinical database is necessary for oncology care management. These data support pathway and guideline adherence, reduce treatment variability, take advantage of emerging companion treatment diagnostics, and promote cost savings through the avoidance of valueless care. In oncology, 6 basic elements are needed to enable such measurement. For every patient, we need to have structured data in the EMR for stage, intent of therapy, toxicity, disease status, patient status, and line of therapy. When there is substantial data density for these 6 process measures, the foundation is in place to begin to measure clinical outcomes across large populations of patients and then, in real time, see what is working.

So how do we get from low density, as presently observed in oncology EMR data, to high density on these process measures? **Figure 1** shows data from an Oncology Metrics survey performed in 2009 and reveals that physicians directly enter most of these data as part of their clinical management activity.

There is ample evidence that peer review does alter physician behavior. Oncologists who received feedback about the amount of chemotherapy that they were giving at the end of life reduced from 50% of patients to 20% of patients in only 6 months.[4] Structured clinical data offer the opportunity to show individuals how they compare with named physicians in their own practice. Additionally, this lets the physician know that others see his score too (**Figure 2**).

Deb Hood, vice president of the national oncology service line of Catholic Health Initiatives (CHI), spoke about the experience of her institution in beginning to establish what she called value-based care metrics. While there are 5 dimensions to their hospital perspective, she emphasized improvement in quality and reduction of cost. Although there are many quality metrics in oncology, CHI has decided to focus on data that are readily available and easy to audit. The best data source for them is registry data, as they are extracted in real time, and encompass more that 30,000 new cases each year. From these data, they have cre-

Figure 2. Sample Process Metric Presented to Physicians

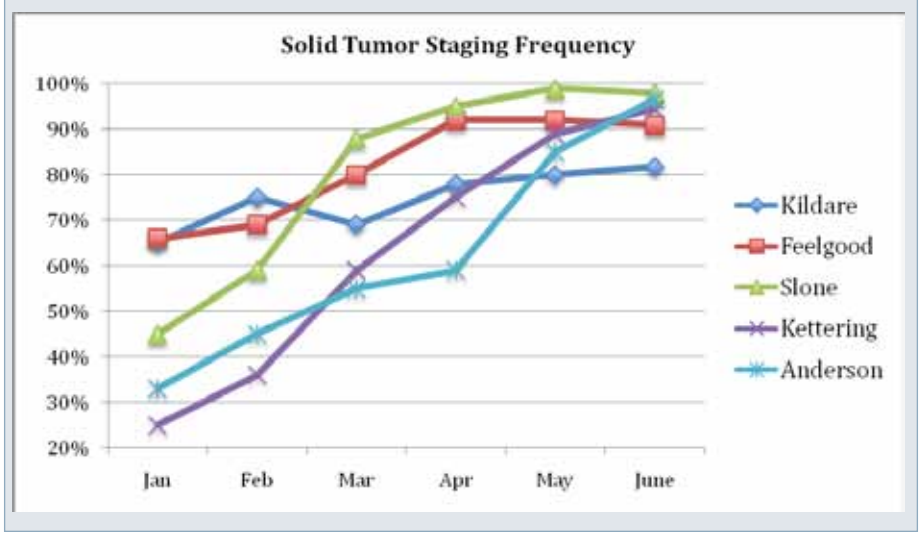


Figure 3. Service Line Dashboard From Catholic Health Initiatives

CATHOLIC HEALTH INITIATIVES®

A spirit of innovation, a legacy of care.

Confidential

National Oncology Service Line Dashboard

Report Run Date: 8/29/12

Senior Vice President:
MBO:
Facility:

At or above Goal | Within 10% of Goal | Beyond 10% of Goal

PEOPLE	Ref. Rate	Available Through	Goal	Prev. Year	Latest YTD	% Change
PEOPLE						
Overall Patient Satisfaction - Outpatient Oncology Services	Q	Jun 30 2012	91.9%	90.63%	91.27%	.64%
Patient Satisfaction with Pain Management.- Outpatient Oncology Services	Q	Jun 30 2012	89.5%	86.23%	85.98%	-.25%
OCN Certified Oncology Nurses	Q	Jun 30 2012	50%	36.27%	34.82%	-1.45%
QUALITY	**Ref. Rate**	**Available Through**	**Goal**	**Prev. Year**	**Latest YTD**	**% Change**
CP3R - ACOS COC						
Radiation therapy is administered within 1 year (365 days) of diagnosis for women under age 70 receiving breast conserving surgery for breast cancer	Q	2010	90%	94.22%	90.58%	-3.64%
Combination chemotherapy is considered or administered within 4 months (120 days) of diagnosis for women under 70 with AJCC T1cN0M0, or Stage II or III hormone receptor-negative breast cancer	Q	2010	90%	90.59%	92.63%	2.04%
Tamoxifen or third generation aromatase inhibitor is considered or administered within 1 year (365 days) of diagnosis for women with AJCC T1cN0M0, or Stage II or III hormone receptor positive breast cancer	Q	2010	90%	88%	84.44%	-3.56%
At least 12 regional lymph nodes are removed and pathologically examined for resected colon cancer	Q	2010	80%	83.97%	87.77%	3.8%
Adjuvant chemotherapy is considered or administered within 4 months (120 days) of diagnosis for patients under the age of 80 with AJCC Stage III (lymph node positive) colon cancer	Q	2010	90%	86.94%	91.1%	4.16%
Radiation therapy is considered or administered within 6 months (180 days) of diagnosis for patients under the age of 80 with clinical or pathologic AJCC T4N0M0 or Stage III receiving surgical resection for rectal cancer	Q	2010	N/A	87.5%	97.5%	10%
PATIENT SAFETY						
Chemotherapy Variances resulting in harm, injury or death	Q	Jun 30 2012	N/A	3	4	N/A
Chemotherapy Variances not resulting in patient harm	Q	Jun 30 2012	N/A	75	73	N/A
Radiation Therapy Variances resulting in (or anticipating result of) harm, injury or death	Q	Jun 30 2012	N/A	1	1	N/A

ated "dashboards" for breast cancer, exception reporting for chemotherapy and radiation therapy, readmission tracking for all oncology patients, and pharmaceutical expense tracking. To leverage these reports to create measurable improvement in care, they are presenting comparative measures at the institutional level with color coding to promote easy understanding. Green is compliant, yellow is nearly in range, and red is out of compliance standard. A sample of such a report card is shown in **Figure 3**.

Wes Chapman, president and CEO of PCD Partners, provided an overview of the application of ISO 9001 and Lean Six Sigma in 2 large-scale projects.[5,6] Noting that outcome metrics are only viable in the context of a uniform process, and understanding that healthcare provision is not at all a uniform process, useful metrics are limited to process metrics (**Figure 4**).

To adequately measure processes in large systems, the integration of documents and data into a single system is necessary. Chapman said that this novel functionality could be created in a cloud-based relational database but noted that these 2 types of information are not standardized. This shortcoming limits the ability of process measurement to provide compelling information about problems addressed and determine if improvements are realized. To achieve process control and improvement, it is necessary to define the process and train process operators, collect process performance data, and then audit process for compliance. None of this functionality is present in large-scale systems today and this is a limiting reality to the application of tested process management technology that is used in the manufacturing environment. To no small degree, this fractioning of healthcare is part of the payment methodology. Fee for service provides incentives for more process steps and leads to variable end points, uncoordinated care, and undocumented outcomes. When healthcare delivery and payment more closely resemble typical manufacturing environments, characterized by a drive to reduce process steps and maximize value, then the tools from that sector will become applicable. **EBO**

Author Affiliation: From Altos Solutions, Neptune Beach, FL.

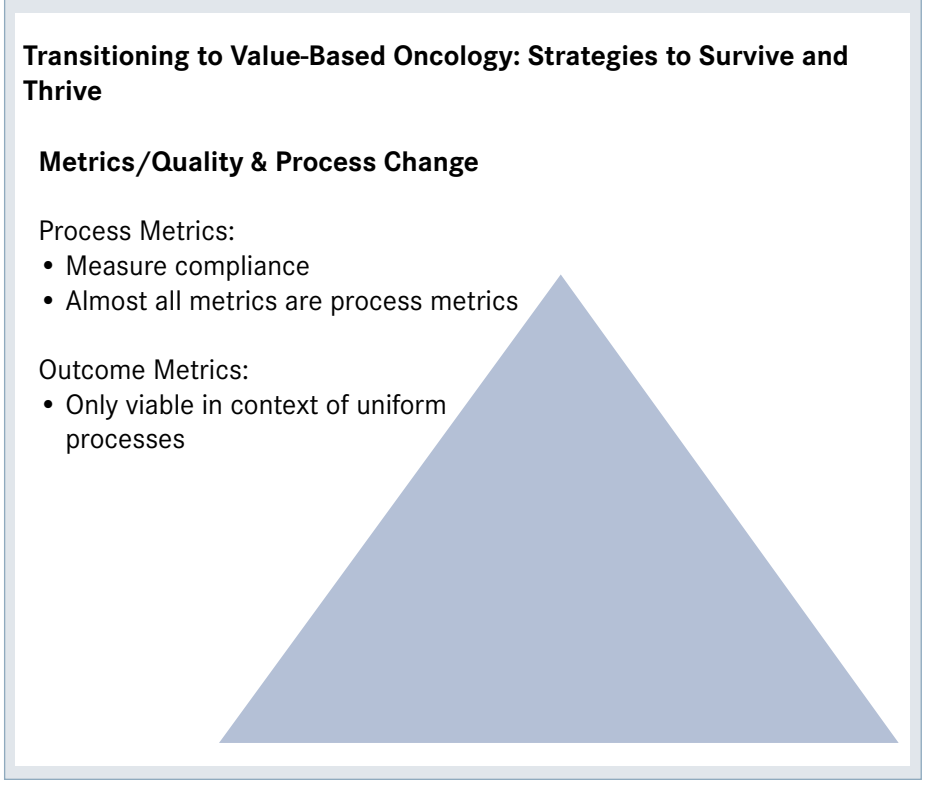
Funding Source: None.
Author Disclosure: The author reports employment with Altos Solutions, which produces electronic health records.
Authorship Information: Concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; provision of study materials or patients; and obtaining funding.

Address correspondence to: Thomas R. Barr, MBA, 520 Hopkins St, Neptune Beach, FL 32266. E-mail: tbarr@oncomet.com.

References

1. EHR incentive programs. Centers for Medicare & Medicaid Services website. www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/index.html. Accessed December 6, 2012.
2. Cancer Center Business Summit website. www.cancerbusinesssummit.com/program.htm. Accessed December 6, 2012.
3. Center for Health Policy Studies, Harvard School of Public Health, Center for Quality of Care Research and Education. Understanding and choosing clinical performance measures for quality improvement: development of typology: final report. Rockville, MD: Agency for Healthcare Research and Quality; 1995.
4. Blayney DW, McNiff K, Hanauer D, et al. Implementation of quality practice initiative at a university comprehensive cancer center. *J Clin Oncol.* 2009;27(23):3802-3807.
5. Bloomberg highlights Vermont cancer pilot; PCD partners plays key HIT role. PCD Systems website. http://pcdsys.com/bloomberg-highlights-vermont-cancer-pilot/. Published August 24, 2012. Accessed December 6, 2012.
6. Decreasing complexity, improving care quality, and reducing cost in oncology. http://pcdsys.com/care-quality-in-oncology/. PCD Systems website. Published July 5, 2012. Accessed December 6, 2012.

Figure 4. Hierarchy of Metrics and the Organizational Sponsors



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

Indication and Important Safety Information for VELCADE® (bortezomib)

INDICATION

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

CONTRAINDICATIONS

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

WARNINGS, PRECAUTIONS, AND DRUG INTERACTIONS

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

In treating multiple myeloma

What is the value of VELCADE® (bortezomib)?

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

IF YOU DEFINE VALUE AS AN OVERALL SURVIVAL ADVANTAGE:

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

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

IF YOU DEFINE VALUE AS DEFINED LENGTH OF THERAPY:

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

IF YOU DEFINE VALUE AS MEDICATION COST:

- Medication cost is an important factor when considering overall drug spend. The Wholesale Acquisition Cost for VELCADE is $1,540 per 3.5-mg vial as of January 2013
- When determining the value of a prescription drug regimen, it may be worth considering medication cost, length of therapy, and dosing regimens. This list is not all-inclusive; there are additional factors to consider when determining value for a given regimen

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

ADVERSE REACTIONS

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

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

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

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

*Melphalan+prednisone.

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

VELCADE®
(bortezomib) FOR INJECTION

VELCADE®
(bortezomib) FOR INJECTION

Brief Summary

INDICATIONS:

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

CONTRAINDICATIONS:

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

WARNINGS AND PRECAUTIONS:

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

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

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

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

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

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

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

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

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

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

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

ADVERSE EVENT DATA:

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

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

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

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

DRUG INTERACTIONS:

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

USE IN SPECIFIC POPULATIONS:

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

Pediatric Use: The safety and effectiveness of VELCADE in children has not been established.

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

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

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

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

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

Takeda MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Millennium Pharmaceuticals, Inc., Cambridge, MA 02139

Printed in USA V-12-0306 11/12

Story Jumper
(continued from ##)

stages, defined as being in the local or regional stages, it has an excellent 5-year survival (nearly 100%) and survival after 15 years is also very high (93%).[2] Ironically, since patients with early-stage prostate cancer experience few or no symptoms, the cancer may not be diagnosed until it has spread to distant areas of the body, including lymph nodes, bones, and other organs. The 5-year survival for patients with metastatic disease is only 28%.[2]

Since the disease is usually diagnosed in older patients, men with slow-growing tumors are frequently monitored using a strategy termed "active surveillance," monitoring the disease and delaying therapy until the disease demonstrates signs of being progressive.[3]

As would be expected, costs associated with the treatment of prostate cancer are greatest (approximately $34,000) in the last year of life. In 2006, the total estimated cost for all prostate cancer care was $9.86 billion.[4] Newer treatments, such as sipuleucel-T, costing more than $93,000 for a full course of therapy, will undoubtedly increase these estimates.[5]

Screening for Prostate Cancer

During the years from 2005 to 2009, the incidence of prostate cancer and number of deaths attributed to it decreased each year. Policy makers speculated that screening with the prostate-specific antigen (PSA) blood test was responsible for the decline.[1] Interestingly, the US Preventive Services Task Force (USPSTF) issued a statement on PSA screening in May 2012 that recommended against PSA-based screening for prostate cancer in the general population. However, it did not apply this recommendation to men who had already been diagnosed with or were being treated for prostate cancer.[6] This recommendation was based on the potential harms of screening, which included:

- High false-positive rate—approximately 100 to 120 of every 1000 men screened may receive an incorrect diagnosis based on the PSA test result, subjecting them to unnecessary biopsies, which could result in undesirable side effects and unneeded worry or anxiety.
- Overdiagnosis—most cancers of the prostate do not grow or cause symptoms. If the tumor does grow, it does so at a slow rate and usually does not cause health problems in the duration of the man's life (based on the older age at diagnosis). The potential for overdiagnosis exists, as current technology cannot differentiate slow-growing tumors from aggressive tumors (a small minority of cases, but life-threatening when they do occur).
- Overtreatment—if more men are diagnosed, it is likely that some proportion of them will undergo active treatment, with potentially deleterious effects.

The Task Force suggested that physicians should not offer PSA testing unless the patient raises the issue, and then the physician discusses with the patient the benefits and potential harms of PSA testing, as well as risks involved with the diagnostic testing and treatment.[7]

Recently, a computer model was used to assess alternative PSA screening strategies. The model evaluated 35 screening strategies that varied by the starting and ending age for screening, screening intervals, and thresholds for recommending a biopsy. Raising the PSA threshold in men aged 50 to 74 years being screened yearly was found to reduce the risk of prostate cancer and the risk for overdiagnosis. In even older men, the risk for prostate cancer was similar to that observed in the men aged between 50 and 74 years, but the risk for overdiagnosis was further reduced. Screening done every other year in men at low risk reduced the risk for prostate cancer and overdiagnosis; moreover, this strategy reduced the number of total tests by 59% and false-positive tests by 50%.[8] This study suggests that screening may not be needed in men older than 70 years, and thresholds for recommending biopsies could be raised in older men. Overall, men with normal PSA levels at baseline may need less-frequent monitoring.[9]

Table 1. Potential Chemoprevention Strategies

Drugs	Vitamins	Other
Finasteride	Vitamn E	Selenium
Dutasteride	Vitamin C	Soy Proteins
Aspirin		Lycopene
Statins		

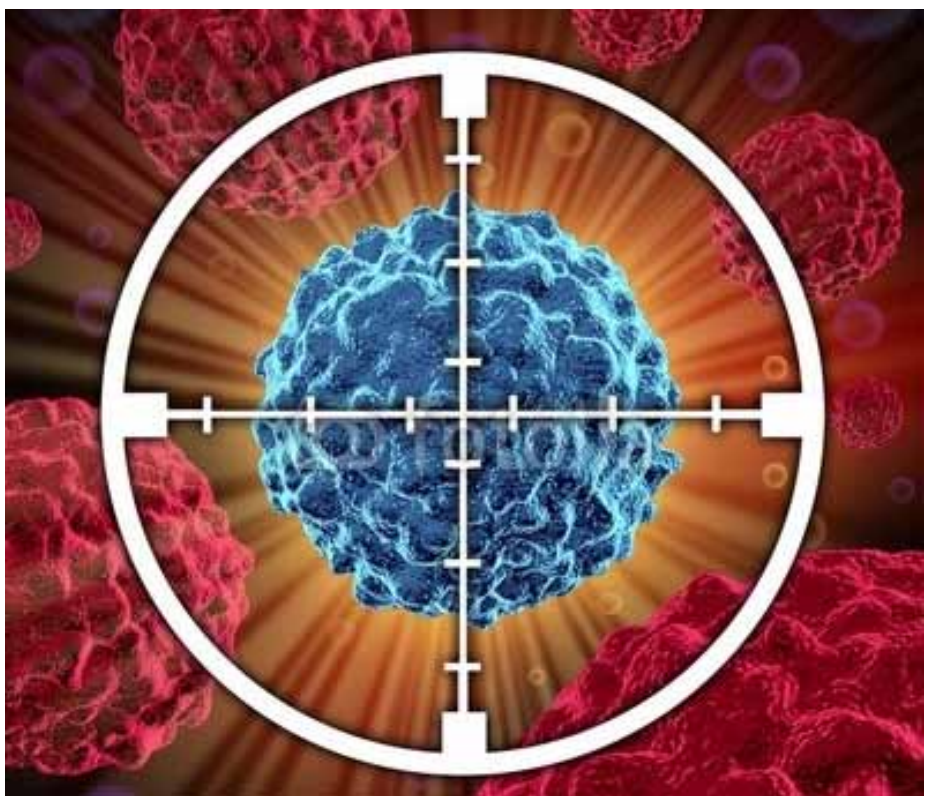
Adapted from Millar LB. What is chemoprevention? OncoLink, March 2011. http://oncolink.org/resources/article.cfm?id=1049. Accessed February 17, 2013.
Abbey C, Al B. Prostate cancer chemoprevention: a current review. *J Cancer Sci Ther*. 2011;100:S3.
Davis J. Current state and future challenges of chemoprevention. *Discov Med*. 2012;13(72):385-390.

The Chemoprevention Controversy

Chemoprevention is the use of drugs, vitamins, or other agents (Table 1) to try to reduce the risk of, or delay the development or recurrence of, cancer as defined by the National Cancer Institute.[10] It is further classified as primary, secondary, and tertiary prevention. Primary prevention refers to preventing the development of cancer, usually in men who have an average or high risk for its occurrence. This includes men with a family history of cancer. Secondary prevention is aimed at individuals with known precancerous lesions. In this case, chemoprevention is used to deter the progression of these lesions to the cancerous state. Tertiary prevention is used in patients with diagnosed prostate cancer to prevent new cancers or metastasis.[11-14] The precancerous state is usually typified by the presence of intra-epithelial neoplasia, which is identified most commonly through biopsy or pathologic samples taken at surgery.[15]

In 2008, the American Society of Clinical Oncology (ASCO) and the American Urological Association (AUA) issued a clinical practice guideline for the use of 5-α-reductase inhibitors (eg, finasteride and dutasteride) for the chemoprevention of prostate cancer (primary prevention only). This guideline was developed based on the results of 15 randomized clinical trials, of which 9 included the prevalence of prostate cancer studies over 1 to 7 years (clinical trial data do not extend beyond 7 years). Only 1 completed trial, the Prostate Cancer Prevention Trial (PCPT), was randomized and was designed to show in a reduction in period-prevalence of prostate cancer. This trial, using finasteride as the intervention, had a very large study population of men who were being actively screened for prostate cancer. The clinical trial REDUCE (Reduction by Dutasteride of Prostate Cancer Events), in which men with a PSA >3 ng/mL were enrolled, was not yet completed at the time of review by the guideline development panel. Thus, the panel knew that additional information would be forthcoming from the REDUCE trial, and that the PCPT trial results would be further analyzed. Neither of these 2 trials was designed to assess the risk of death resulting from prostate cancer. The primary objective of both of these clinical trials was to study the safety and efficacy of drugs indicated for the treatment of benign prostatic hyperplasia (BPH).

The panel concluded that therapy with a 5-α-reductase inhibitor during a 7-year period would lead to a 25% relative risk reduction (but only a 1.4% absolute risk reduction) for a prostate cancer diagnosis. The panel noted an increase in high-grade cancers, but they believed it was doubtful that this could occur while there was also a decrease in low-grade tumors. However, since men are prescribed 5-α-reductase inhibitors for BPH and male pattern baldness, they recommended that this potential finding should be discussed with these respective patients. Additionally, they knew that data from the REDUCE trial would support or dispute the findings of the presence of in-



THE AMERICAN JOURNAL OF MANAGED CARE

Table 2. Effects of Chemoprevention in 2 Major Clinical Trials

	PCPT Trial	REDUCE Trial
Relative Risk of Prostate Cancer	Decreased 25%	Decreased 23%
Absolute Risk of Prostate Cancer	Decreased 6%	Decreased 5%
Absolute Risk of High-Grade Prostate Cancer	Increased 0.6%	Increased 0.5%

PCPT indicates Prostate Cancer Prevention Trial; REDUCE, Reducation by Dutasteride of Prostate Cancer Events.

creased high-grade prostate cancer in men receiving a 5-α-reductase inhibitor.

The suggestion from the panel was that men with a PSA level below 3.0 ng/mL who agreed to annual PSA screening might benefit from 5-α-reductase inhibitor therapy for a period of 7 years. Men should also be made aware of the potential benefits and risks of such therapy by their physicians.[11]

The results of the REDUCE trial were similar to those seen in the PCPT trial (Table 2). There was a decrease in relative risk and absolute risk for developing prostate cancer when using 5-α-reductase inhibitor therapy, but there was in increase in the absolute risk for the development of high-grade prostate cancer. The original publication of the trial did not show an increased risk for high-grade prostate cancer, but the FDA mandated a reanalysis of the data using a modified scoring scale which resulted in an increase in high-grade prostate cancer.[16]

In December 2010, the Oncologic Drugs Advisory Committee voted against approving dutasteride and finasteride for the prevention of prostate cancer based on the findings of the REDUCE and PCPT trials. The FDA followed the committee's recommendation in January 2011.[17] Since the FDA did not approve the drugs for the prevention of prostate cancer, ASCO and AUA subsequently archived the 2008 clinical guideline on the use of 5-α reductase inhibitors for prostate cancer chemoprevention. However, the guideline is available in the "Archived Guides" section of the AAU website.[18]

The AUA communicated that it believes some urologists and urologist-oncologists would continue to prescribe these medications for men at potentially high risk for prostate cancer and that these agents should be used with caution. It believed the decision was controversial and still debatable.[18]

The Southwestern Oncology Group (SWOG) disagreed with the FDA's decision, saying that it believed the PCPT reanalysis demonstrated that the use of 5-α-reductase inhibitors could significantly reduce the risk of prostate cancer.[19] Even the USPSTF concluded that additional studies were needed to determine the impact of 5α-reductase inhibitors on the mortality of men with prostate cancer.[20] Furthermore, a reanalysis of the data from the PCPT and REDUCE trials for mortality suggested there may have been a small increase in deaths due to therapy, but that there could have also been a modest decrease.[21]

Coupled with the clinical analysis of the use of 5-α-reductase inhibitors for the chemoprevention of prostate cancer, several investigators examined the cost-effectiveness and cost utility of using these drugs specifically for chemoprevention. A study in the mid-2000s utilizing a Markov decision analysis model concluded that prescribing finasteride in a lower-risk population ≥50 years would not be cost-effective; however, if it were used in men with a high risk for prostate cancer (defined as at least 50 years of age with a probability of at least 30% for developing prostate cancer), the chemoprevention strategy could be cost-effective. If the lifetime prevalence were to be increased, the costs per life-year saved would be reduced; moreover, the cost of the chemoprevention strategy would also affect the costs.[22] Another study utilizing a Markov decision analysis model also concluded that finasteride would not be likely to be cost-effective for use in the general population, but that it would be cost-effective to prescribe it in high-risk men (defined as ≥50 y and a ≥30% chance of developing prostate cancer), especially if quality-of-life issues (erectile dysfunction, loss of libido, and incontinence) were considered. The sensitivity analysis showed a cost-effectiveness ratio of <$50,000 per QALY with a 25% risk reduction in the men at high risk.[23] There appears to be a level of agreement that utilizing these medications in low-risk populations would not be cost-effective, but that there is a cost benefit to their use in high-risk men.[24-27]

Age alone (ie, men older than 50 years) does not appear to be the only criterion for initiating chemoprevention. Assuming that finasteride use resulted in a constant risk reduction for all tumor grades, the drug was found not cost-effective because of the costs associated with side effects (urinary and bowel incontinence, impotence, and erectile dysfunction).[28] A Markov model has been developed that shows high-risk men, defined as those having a positive family history and the presence of genetic markers for prostate cancer, would benefit from chemoprevention.[29]

What Exactly Is the Focus of the Debate?

There is little question that PSA testing at present is a useful tool, but has been an overused one, in our limited arsenal to screen for prostate cancer. And when it is used appropriately, there is little consensus (except in cases of extreme readings) on how to interpret the results. Many even argue that the logic in favor of screening is faulty, owing to the relatively slow growth of early-stage prostate tumors. However, few would not want to prevent late-stage prostate cancer and seek to improve its poor 5-year survival.

Therefore, the real debate seems not to address the value of preventing prostate cancer but whether our technologies for prevention (both screening and treatment) are efficient enough to yield cost-effective outcomes. If 5-α-reductase inhibitors are not sufficiently effective in preventing the development of prostate cancer, or if the side effects of the medications are such that the costs to treat (or in terms of reduced quality of life) result in inadequate cost-effectiveness, are there specific patients where the drugs may be useful and are there more effective chemoprevention strategies available or on the horizon?

The debate about the use of 5-α-reductase inhibitors as chemoprevention for prostate cancer continues, as does the utilization of PSA testing to screen men for the disease. Based on the sheer numbers of men who develop prostate cancer and the cost burden of the disease, it seems that the need exists for both a useful screening tool and a chemoprevention strategy. Appropriate application of this strategy will be the key to success. Evolving and improved technology will be paramount in making this happen. **EBO**

Funding Source: None.

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

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

References

1. American Cancer Society. Cancer Facts & Figures 2013. Atlanta: American Cancer Society; 2013.

2. American Cancer Society. Prostate Cancer 2013. Atlanta: American Cancer Society; 2013. www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics. Accessed January 29, 2013.

3. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed January 29, 2013.

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

5. Mulkhy N. Medicare already paying for Provenge for some patients: national coverage analysis still important. Medscape Medical News, January 6, 2011. www.medscape.com/viewarticle/735366. Accessed January 30, 2013.

6. Screening for prostate cancer. US Preventive Services website. www.uspreventiveservicestaskforce.org/prostatecancerscreening.htm. Published 2012. Accessed February 17, 2013.

7. Talking with your patients about screening for prostate cancer. US Preventive Services website. www.uspreventiveservicestaskforce.org/prostatecancerscreening/prostatecancerscript.pdf. Published 2012. Accessed January 29, 2013.

8. Gulati R, Gore JL, Etzioni R. Comparative effectiveness of alternative prostate-specific antigen-based prostate cancer screening strategies: model estimate of potential benefits and harms. *Ann Intern Med.* 2013;158(3):145-153.

9. American College of Physicians. Summaries for patients: screening smarter, not harder, for prostate cancer. *Ann Intern Med*. 2013;158(3):1-30. http://annals.org/article.aspx?articleid=1567366. Accessed February 18, 2013.

10. NCI dictionary of cancer terms. National Cancer Institute website. www.cancer.gov/dictionary?cdrid=45487. Accessed January 30, 2013.

11. Kramer BS, Hagerty KL, Justman S, et al. Use of 5-α-reductase inhibitors for prostate cancer chemoprevention: American society of clinical oncology/American urological association 2008 clinical practice guideline. *J Clin Oncol.* 2009;27(9)1502-1516.

12. Abbey C, Al B. Prostate cancer chemoprevention: a current review. *J Cancer Sci Ther.* 2011;100:S3.

13. Davis, J. Current state and future challenges of chemoprevention. *Discov Med.* 2012;13(72):385-390.
14. Millar LB. What is chemoprevention? OncoLink 2011. www.oncolinkorg/resources/article/cfm?id=1049. Accessed January 30, 2013.
15. Bostwick DG, Qian J. High-grade prostatic intraepithelial neoplasia. *Mod Pathol.* 2004;17:360-379.
16. Violette PD, Saad, F. Chemoprevention of prostate cancer: myths and realities. *J Am Board Fam Med.* 2012;25(1):111-119.
17. Chustecka Z. Dutasteride not approved for prostate cancer prevention. Medscape Medical News Oncology News, January 28, 2011. www.medscape.com/viewarticle/736465. Accessed January 30, 2013.
18. The New Prostate Cancer Infolink. AUA and ASCO to "archive" clinical guidance of use of 5-ARIs for prostate cancer prevention. http://prostatecancerinfolink.net/2012/12/03/aua-and-asco-to-archive-clinical-guidance-of-use-of-5-aris-for-prostate-cancer-prevention/. Published December 3, 2012. Accessed January 30, 2013.
19. SWOG Newsletter. FDA's ODAC votes no, loudly, on finasteride for prostate cancer prevention. http://swog.org/visitors/newsletters/2010/12/index.asp?a=spotlight. Published December 2010. Accessed January 31, 2013.
20. Moyer VA on behalf of the US Preventive Services Task Force. Screening for prostate cancer: United States Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2012;157(2):120-134.
21. Pinsky PF, Black A, Grubb R, et al. Projecting prostate cancer mortality in the PCPT and REDUCE chemoprevention trials. *Cancer.* 2013;119(3):593-601.
22. Svatek RS, Lee JJ, Roehrborn CG, et al. The cost of prostate cancer chemoprevention: a decision analysis model. *Cancer Epidemiol Biomarkers Prev.* 2006;15(8):1485-1489.
23. Svatek RS, Lee JJ, Roehrborn CB, et al. Cost-effectiveness of prostate cancer chemoprevention: a quality of life-years analysis. *Cancer.* 2008;112(5):1058-1065.
24. Earnshaw SR, McDade CL, Black LK, Bell CF, Kattan MW. Cost effectiveness of 5-alpha reductase inhibitors for the prevention of prostate cancer in multiple patient populations. *Pharmacoeconomics.* 2010;28(6):489-505.
25. Zeliadt SB, Ramsey SD. Cost-effectiveness of prostate cancer chemoprevention among high-risk men. *Expert Rev Pharmacoecon Outcomes Res.* 2010;10(5):505-508.
26. Svatek RS, Lotan Y. Cost utility of prostate cancer chemoprevention with dutasteride in men with an elevated prostate specific antigen. *Cancer Prev Res.* 2011;4(2):277-283.
27. Kattan MW, Earnshaw SR, McDade CL, Black LK, Andriole GL. Cost-effectiveness of chemoprevention for prostate cancer with dutasteride in a high-risk population based on results from the REDUCE clinical trial. *Appl Health Econ Health Policy.* 2011;9(5):305-315.
28. Stewart SB, Scales CD, Moul JW, Reed SD. Does variation in either age at start of therapy or duration of therapy make chemoprevention with finasteride cost-effective? *Prostate Cancer Prostatic Dis.* 2012;15(4):380-385.
29. Reed SD, Scales CD, Stewart SB, et al. Effects of family history and genetic polymorphism on the cost-effective of chemoprevention with finasteride for prostate cancer. *J Urol.* 2011;185(3):841-847.

Payer Perspective
Interview With Paul Handel, MD

The Need to Stress Primary Prevention Is a Huge Opportunity in Prostate Cancer

EBO: **At this point in time, what are your personal impressions of prostate-specific antigen (PSA) screening overall?**
Dr Handel: I am a urologist. In the pre-PSA test era, most cases of prostate cancer were detected in advanced stages, which precluded curative management. The benefits of the screening have been eclipsed but not negated by the overly aggressive technological approach to testing. With appropriate age limitations, health status evaluation, and shared decision making, the PSA testing remains a valuable screening test. I am not aware of any current testing modalities that would replace the PSA test in combination with a digital rectal examination.

EBO: **What are HCSC's recommendations regarding prostate cancer screening?**
Dr Handel: We leave it to the discretion of the treating physician and the patient. We don't have internal guidelines in this area. Our own recommendations are reflective of the American Urological Association, National Comprehensive Cancer Network, and other guidelines.

EBO: **How would you characterize current prostate cancer screening efforts today?**
Dr Handel: Current screening efforts have been confused by the US Preventive Services Task Force (USPSTF) recommendations. There is confusion about when to start and stop the screenings. Generally, the frequency of testing (yearly) has not been an issue. The larger question is what next steps should be followed after a positive PSA test is revealed. The urologic community needs, and is working on, guidelines for intervention. An additional consideration needs to be the medicolegal implications, mandating full consent and possibly tort reform.

The major shortcomings of screening efforts today have been in the relatively indiscriminate testing based on age and physical condition. Additionally, many patients and doctors forgo a digital rectal exam, relying on the PSA test results alone for screening.

In contrast, a huge overlooked opportunity relates to the preventive aspect. It is rare to see recommendations about physical activity and dietary changes to help reduce the potential for prostate cancer.

EBO: **There has been a bit of controversy surrounding the use of chemoprevention (ie, finasteride, dutasteride, other agents) in prostate cancer. Does HCSC cover the use of these agents for primary prevention (general population or those with BPH) and secondary prevention (high-risk patients—those in whom interstitial neoplasia has been found)?**
Dr Handel: Since HCSC does not have any UM requirements for finasteride or dutasteride, we would not know if these agents are being prescribed off-label for primary or secondary prevention of BPH. As a result, these agents could be covered for chemoprevention. As you are aware, the NCI Prostate Cancer Prevention Trial showed a positive benefit of reducing the incidence of prostate cancer with the use of finasteride for chemoprevention, but there also was a statistically significant increase in the percentage of high-grade prostate cancers. This risk, combined with the side effect profile of these drugs, will continue to limit their use to only high-risk patients.

EBO: **Do you believe the preventive benefit of these agents outweigh the side effects associated with the 5-α-reductase inhibitors (finasteride and dutasteride)?**
Dr Handel: Yes, in the appropriate patients. Their side effects are relatively mild and occur in perhaps 5% of the patients treated. Initiating therapy and then stopping it based on side effects is not unreasonable.

EBO: **How do you think prostate cancer chemoprevention will change by the year 2025?**
Dr Handel: Most likely in the use of novel antiandrogens or androgen-receptor blocking agents.

EBO: **As a health plan executive, where do you see the greatest value in prostate cancer today?**
Dr Handel: Two areas emerge immediately: First, the primary prevention must be stressed! Again, these concentrate on animal fat restriction and increased physical activity.

Second, closer adherence to diagnostic and therapeutic guidelines would benefit patients.

EBO: **Where would you like to see more comparative effectiveness research done in this area?**
Dr Handel: I believe the Holy Grail may be better identification of the cohort of patients who will benefit from treatment.

Dr Handel is senior vice president and chief medical officer at Health Care Service Corporation in Chicago, IL.

This is the biologic medicine

That the patient counts on

That the nurse trusts

That the pharmacist has confidence in

That the doctor relies on

Because it was manufactured knowing the patient's treatment depends on it.

Building confidence in the quality and supply of biologic medicines starts with a deeper understanding of how these medicines are made.

After all, there's so much at stake.

That's why manufacturing matters.

Learn more at
buildingbiologics.com

An educational initiative from AMGEN®