



## Evidence-Based Oncology

### Healthcare Delivery

## The Future of Oncology? COME HOME, the Oncology Medical Home

Barbara L. McAneny, MD



Barbara L. McAneny, MD

Oncology care is in the spotlight for health system reform. As the baby boomers age, we will see an increase in the number of cancer patients. Cancer patients are living longer, which requires more oncology visits, more treatment, and therefore more money. The problem is that healthcare already consumes 17% of gross domestic product.

Dr Donald Berwick inspired many of us to hunt for the Triple Aim: better health, better healthcare, and lower costs. My Innovation Center grant, COME HOME (Community Oncology Medical HOME), was developed to meet the Triple Aim by working on

the parts of the healthcare system that physicians can actually control—the site of service and the care we give.

It is becoming recognized by many, including MEDPAC, that there is a significant differential in the cost of care when paid for through the Hospital Outpatient Prospective Payment System rather than through the Physician Fee Schedule. Many

*(continued on page 41)*

### Clinician Interview

## Focusing on Clinical and Economic Outcomes—Not Guidelines

### Is It Time for a New Direction in Oncology Care?

Interview With Andrew Pecora, MD, CPE, President, Regional Cancer Care Associates, Chief Innovations Officer and Vice President, Cancer Services, John Theurer Cancer Center at Hackensack University Medical Center

### EBO: What's your opinion today about the state of oncology care and payment?

**Dr Pecora:** Oncology is at a crossroads—more people are living longer, and therefore, more people will develop cancer, which means that we are using more drugs and surgical technologies to keep people alive longer. This means oncology care is getting more expensive, and on a macro level, this contributes significantly to increasing healthcare expenditures. Over time, some cancer care may become unaffordable, which could lead to the need to ration care—and that would be tragic. At this crossroads, we have to do something that allows us to modulate the growth of the cost of cancer care while avoiding rationing.



Andrew Pecora, MD, CPE

*(continued on page 43)*

### Diagnostic Testing Personalized Medicine

## The Role of Companion Diagnostic Testing in Payer Decision Making

Jerry Conway

As the saying goes, “When one door closes, another door opens.” And for the pharmaceutical industry, that translates to a transformation toward targeted therapies over the



Jerry Conway

one-size-fits-all, blockbuster model of drug development and commercialization.

Despite the best efforts of the pharmaceutical industry to develop potentially curative approaches to diseases, such as cancer, many patients fail to respond to standard therapies, experience adverse events, or develop resistance to prescribed treatments. Payers have developed many strategies to effectively manage this reality, including the development of formularies, pathways, differential copayments, and support for generics; however, the process has been a continuous challenge.

As the pharmaceutical industry adjusts to the current patent cliff and an increasingly payer-driven environ-

*(continued on page 44)*

### Also in this issue...

SP19 Crossroads in Breast Cancer: The Intersection of Clinical Uncertainty and Molecular Profiling

SP24 Managed Care Restrictions: Barriers to Product Use in Cancer Care

SP26 Partial Fill Strategies for Oral Oncolytics to Reduce Waste and Drive Persistence

SP32 From Bench to Bedside: Promising Colon Cancer Clinical Trials



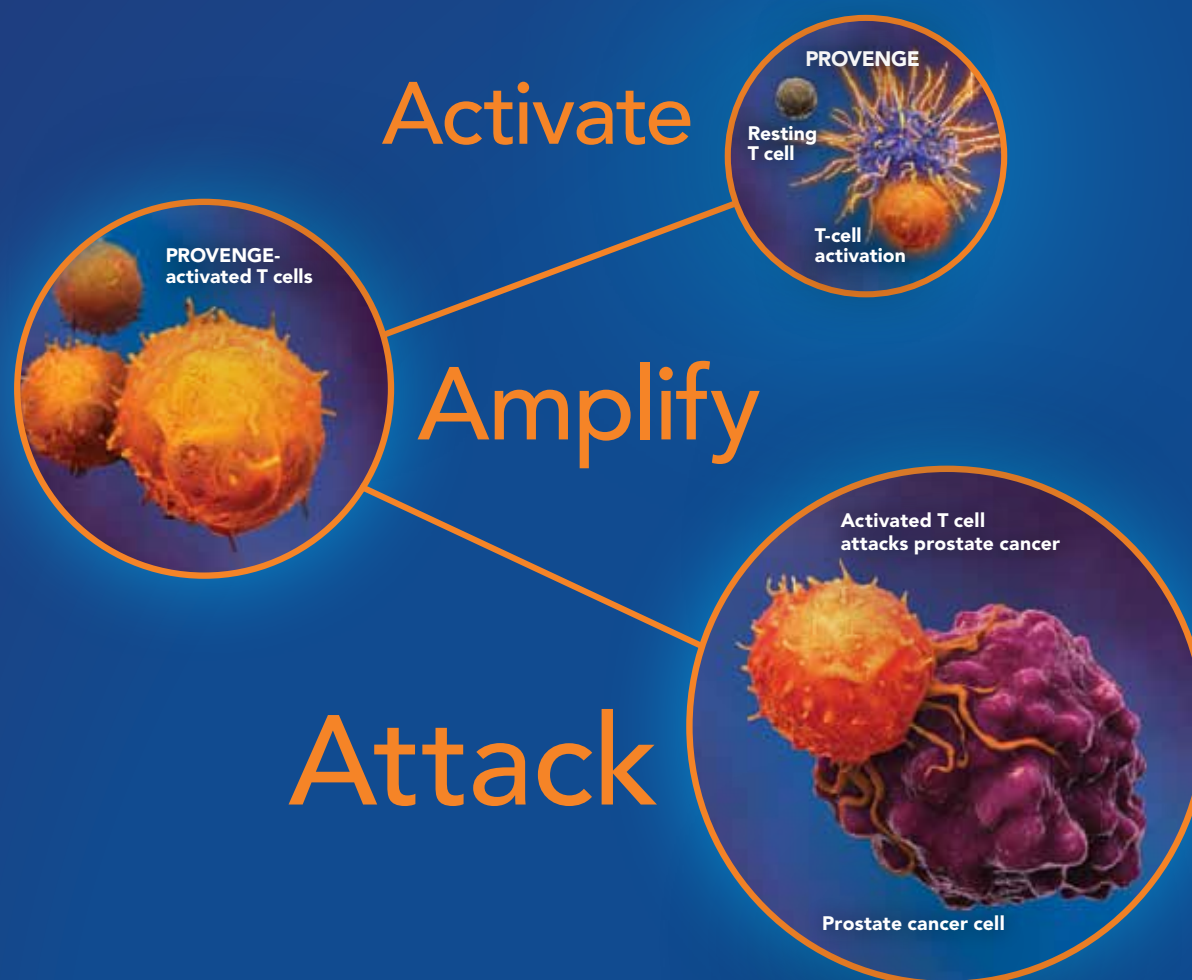
Bruce Feinberg, DO, Speaks About Clinical Pathways in Oncology Care



Peter Bach, MD, MAPP, Talks About Improving Quality in Cancer Care

In advanced prostate cancer

# TREAT FIRST LINE WITH PROVENGE TO



## EXTEND SURVIVAL

> 2<sub>years</sub>

Extends median survival beyond 2 years<sup>1</sup>

1<sup>st</sup><sub>and only</sub>

First and only FDA-approved immunotherapy for advanced prostate cancer

1<sup>st</sup><sub>line</sub>

First-line treatment for men with asymptomatic or minimally symptomatic metastatic CRPC (NCCN Category 1 recommendation)<sup>2</sup>

**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  $\geq 15\%$ ) 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](http://www.PROVENGE.com)

**PROVENGE**<sup>®</sup>  
(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  $\geq 15\%$ , 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  $\leq 1$  day following a leukapheresis procedure in  $\geq 5\%$  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  $\geq 5\%$  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  $\geq 5\%$  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 (%)
<b>Any Adverse Event</b>	<b>591 (98.3)</b>	<b>186 (30.9)</b>	<b>291 (96.0)</b>	<b>97 (32.0)</b>
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](http://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](http://www.nccn.org). Accessed April 26, 2012.

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Targeting Cancer, Transforming Lives®

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**PROVENGE**  
(sipuleucel-T)

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Over the next 12 months, our healthcare industry is going to experience mass change. Organizations will continue to implement strategies and processes that comply with new health reform laws. Although this is no easy task, the hope is that all of these efforts will lead to healthcare that is more accessible and affordable—2 essential components of cancer care.

This issue of *Evidence-Based Oncology* features several articles by healthcare professionals who are working to transform the delivery of healthcare in oncology. Barbara L. McAneny, MD, New Mexico Oncology/Hematology Associates, discusses some of the challenges that go into the creation of a successful oncology medical home. “Oncology care is in the spotlight for health system reform,” writes Dr McAneny, whose Innovation Center grant, COME HOME (Community Oncology MEDical HOME), is aimed at helping community oncology practices provide quality care at a lower cost in a setting more convenient to patients.

John Fox, MD, MHA, Priority Health, also writes about the evolution of the oncology medical home, something he says “represents an intermediate space where community oncologists and payers can work collaboratively on Triple AIM goals.” He notes that the first key element to running a successful oncology medical home is setting up a payment reform model that facilitates care transformation from a purely fee-for-service method to an increasingly performance- and outcomes-based system. Dr Fox also describes Priority Health’s 2-year oncology medical home program developed and implemented in February 2011.

Also in this issue, Andrew L. Pecora, MD, chief innovations officer and vice president of cancer services, John Theurer Cancer Center, talks about oncology care payment models, which are at a crossroads. He mentions some of the challenges and benefits related to integrated delivery systems. Dr Pecora is very knowledgeable in this area, as he is also president of Regional Cancer Care Associates, a statewide group of 76 oncologists that have consolidated their practices in an effort to lower costs and combine resources for more than 33% of New Jersey’s cancer patients.

In addition to the aforementioned features, this issue contains a number of other resources, such as a comprehensive overview of the colorectal cancer pipeline, as well as conference coverage from the American Society of Hematology and San Antonio Breast Cancer Symposium conferences.

An unprecedented era of healthcare delivery is under way. In addition to an increase in federal regulations, technological advancements are occurring at a rapid pace. Despite the burden that an ever-evolving healthcare landscape and marketplace may put on individuals and organizations that are trying to stay ahead of the curve, there is also an element of excitement, as new payment models and technological processes have the potential to make healthcare more accessible and affordable to those that need it the most. Many of these new payment models were discussed by the nation’s premiere thought leaders at *The American Journal of Managed Care’s* inaugural live meeting, “Translating Evidence-Based Research into Value-Based Decisions in Oncology,” this past November. We are happy to announce that videos of these presentations are now available online at [www.ajmc.com/livemeeting](http://www.ajmc.com/livemeeting).

Equally as important as evolving payment models are the ongoing discussions to determine the best value for healthcare services, and our newly forged partnership with the *Center for Value Based Medicine* promises to further those discussions.

Keeping up with all the issues related to oncology care has become more time-consuming than ever. As always, our aim is to provide you with print and digital resources to help you stay abreast of the latest news and research in cancer care. Thank you for reading.

Brian Haug  
Publisher

## EDITORIAL MISSION

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

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## In This Issue...

**SP5 HEALTHCARE DELIVERY**  
Lessons From an Oncology Medical Home Collaborative



*Despite the allure of ACOs to payers, most private oncology practices do not have the risk-based capital or the experience at present to successfully participate.*

**SP12 LITERATURE REVIEW**  
Chronic Myeloid Leukemia



*NCCN guidelines do not factor cost into the treatment consideration. In other words, the guidelines are suggestive but are not sufficiently prescriptive for providers or payers to take action based on the results of cytogenetic testing.*

**SP16 LITERATURE REVIEW**  
Melanoma

**SP19 SABCS CONFERENCE COVERAGE**  
Crossroads in Breast Cancer: The Intersection of Clinical Uncertainty and Molecular Profiling

**SP21 ASH CONFERENCE COVERAGE**  
Newly Discovered Biomarkers Predict Response in AML

Evidence-Based Approaches to Cytopenias Discussed

**SP24 ONCOLOGY MANAGEMENT**  
Managed Care Restrictions: Barriers to Product Use in Cancer Care

**SP26 MEDICATION ADHERENCE**  
Partial Fill Strategies for Oral Oncolytics to Reduce Waste and Drive Persistency



*An analysis of patients diagnosed with early-stage breast cancer showed that less than 50% of patients prescribed adjuvant hormonal therapy actually continued therapy for the full duration of the optimal schedule for treatment.*

**SP32 COLORECTAL CANCER PIPELINE**  
From Bench to Bedside: Promising Colon Cancer Clinical Trials

**SP41 HEALTHCARE DELIVERY**  
The Future of Oncology? COME HOME, the Oncology Medical Home



*My theory is that these systems don't work because the person trying to coordinate care is not part of the practice that is managing the patient.*

**SP43 CLINICIAN INTERVIEW**  
Focusing on Clinical and Economic Outcomes—Not Guidelines

*Is It Time for a New Direction in Oncology Care? Interview With Andrew Pecora, MD, CPE, President, Regional Cancer Care Associates, Chief Innovations Officer and Vice President, Cancer Services, John Theurer Cancer Center at Hackensack University Medical Center*

**SP44 COMPANION DIAGNOSTICS**  
The Role of Companion Diagnostic Testing in Payer Decision Making

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# Lessons From an Oncology Medical Home Collaborative

John Fox, MD, MHA



PatientCenteredMedicalHomePCMH.aspx). There are a number of attributes of the medical home, including access to care, patient engagement, care coordination, team-based care, decision support, and physician feedback, which are equally relevant and germane to oncology practices.

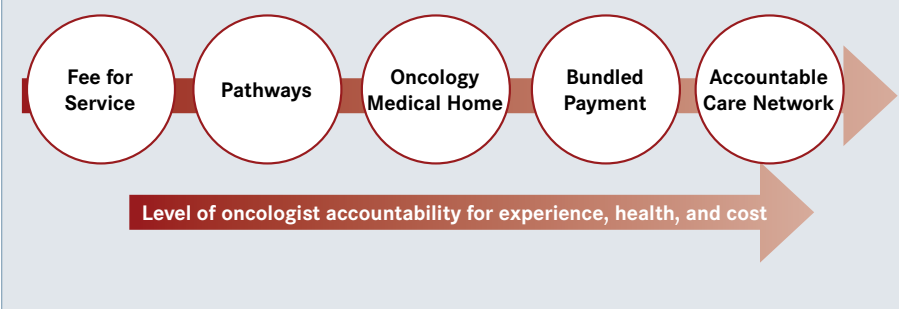
In collaboration with community-based oncology practices, Priority Health, a regional Michigan-based insurance carrier, developed and implemented a 2-year oncology medical home program in February 2011. The core purpose of this program was to drive oncology patient care delivery redesign through the adoption of the oncology medical home and in doing so achieve Triple Aim objectives. Community oncologists were chosen as a partner because prevailing evidence shows these are the most cost-effective settings in which to provide cancer care.<sup>4,5</sup>

The program, which now includes more than 60 physicians in 6 practices, embodies the 3 core elements of payment reform, care redesign, and measurement:

1. The practice agrees to develop and measure adoption of key elements of an oncology medical home model: a) adherence to preferred regimens for high-volume conditions, b) care enhancement including patient education and engagement and triage initiatives, c) advance care planning (ACP), and d) survivorship planning.
2. Priority Health agrees to pay a) a monthly care management fee for patients receiving active oral and/or infused chemotherapy, b) drug acquisition costs, c) an annual infrastructure payment, d) enhanced fees for ACP, treatment planning, genetic counseling, and other agreed-upon services, and e) a shared savings for reductions in emergency department (ED) encounters and hospitalizations.
3. The practice and Priority Health agree to adopt performance metrics to assess patient experience, health outcomes, and per capita utilization.

Since a core tenet of the program was to drive sustainability of community-based oncology practices, eligibility required practices to infuse chemotherapy in a private office setting, to

**Figure. Models for Oncologist Compensation and Accountability for Triple Aim Outcomes**



be open to all products offered in the geographic area, and to have provided evaluation and management services to at least 10 Priority Health members in the preceding 12 months.

## Payment Reform

The first key element in the OMH initiative centers on payment reform. To facilitate care transformation from a purely fee-for-service method to an increasingly performance- and outcomes-based system, the practices and the plan agreed to a 5-part payment reform strategy. This included drug reimbursement, care management, shared savings, infrastructure development, and enhanced services. These are outlined in the following section.

## Payments: Drug Reimbursement

Through the OMH program, all eligible intravenous and oral drugs administered and billed by the practice will be paid at the practice's acquisition cost, as mutually agreed upon by the practice and Priority Health. In essence, practices are no longer paid margins on drugs. Rather, they are paid a monthly case management fee (see below). This, in effect, separates the oncologist's income from drug choice while enhancing the ability to comply with oncologist-developed preferred treatment regimens and other elements of an oncology medical home.

Typically the practice's acquisition costs are a small percentage above ASP. This reflects the delay between price increases experienced by practices and the delay in reflecting those prices in the ASP. By mutual agreement, we did not factor rebates received by practices into the acquisition price because the net value of rebates has fallen dramatically and because incorporating them

into net acquisition cost calculations would be difficult to operationalize. In most circumstances, acquisition cost estimates were independently verified by a neutral third party ([www.iononline.com](http://www.iononline.com)).

## Payments: Care Management Fee

The practices and the plan agreed to a monthly care management (CM) fee for patients receiving active chemotherapy, including oral and IV therapy, in lieu of payment for margins on drugs. The fee is independent of cancer type or method of drug administration (oral or IV), although the actual CM fee varies by insurance product. For example, commercial fees are in the \$200 to \$250

*Despite the allure of ACOs to payers, most private oncology practices do not have the risk-based capital or the experience at present to successfully participate.*

per month range, while Medicare and Medicaid fees range between \$50 and \$100 per month.

In order to pay the care management fee, a working definition of active che-

The past decade has witnessed a proliferation of oncology cost-control initiatives, primarily through the use of chemotherapy pathways programs.<sup>1</sup> Pathways programs form part of a natural progression away from fee-for-service practice to bundled payments and accountable care organizations (ACOs; **Figure**), where oncologists are increasingly accountable for Triple Aim measures of patient experience, individual and population health outcomes, and costs. Pathways programs are limited because the focus is on controlling costs rather than outcomes and experience. Bundled payment models and ACOs have received significant attention.<sup>2,3</sup> Yet despite the allure of ACOs to payers, most private oncology practices do not have the risk-based capital or the experience, at present, to successfully participate. This article describes the oncology medical home (OMH) model, which represents an intermediate space where community oncologists and payers can work collaboratively on Triple Aim goals.

The OMH model of care for patients with cancer is a natural evolution of provider-payer partnerships around the primary care patient-centered medical home (PCMH) model. PCMH is a model of care provided by physician practices aimed at strengthening the physician-patient relationship by replacing episodic care, based on illnesses and patient complaints, with coordinated care in a long-term healing relationship ([www.ncqa.org/Programs/Recognition/](http://www.ncqa.org/Programs/Recognition/)

## Sidebar A. Eligibility for Care Management Fee

Members are eligible for the care management fee if they are:

1. Active Priority Health members for any product (HMO, POS, MCD, MAPD, PPO). Members are immediately eligible; there is no defined minimum time period for eligibility (eg, 6 months). This applies to patients who have Priority Health as either a primary or secondary insurer
2. Receiving active infused or oral chemotherapy—independent of when they started—in the office or home setting
  - a. If a patient became a Priority Health member in the middle of therapy, he or she is still eligible
  - b. All patients on chemotherapy are eligible, not simply those on a “preferred regimen” protocol
3. Admitted to the hospital for complications unless also receiving chemotherapy
4. Receiving palliative care services and chemotherapy
5. Enrolled in a clinical trial and receiving chemotherapy in the office setting

Members are ineligible for the care management fee for a calendar month if during that calendar month they:

1. Receive only selected drugs for maintenance chemotherapy (eg, tamoxifen)
2. Receive chemotherapy in the hospital
3. Receive chemotherapy in a non-office, non-home setting (eg, hospital outpatient or infusion center)
4. Do not receive chemotherapy
5. Receive only radiation therapy

motherapy was collaboratively developed. Active chemotherapy is defined as oral or IV administration of a cytotoxic, cytostatic, or biologic agent intended to treat cancer. A list of eligible drugs is maintained by the plan and periodically reviewed by the practices. It includes J9999 (antineoplastic drugs

***In contrast, if practices are only 70% compliant with NCCN or 60% compliant with practice-developed preferred regimens, then practices receive only 20% of the net savings.***

not otherwise classified), which is often used for new oncology agents. The parties agree to exclude some regimens considered maintenance chemotherapy, including oral anti-estrogen hormonal agents (eg, Aromasin, Arimidex), from the case management fee while

including others such as maintenance chemotherapy for multiple myeloma.

A prevailing theme during discussions with physicians was a desire to be paid for their cognitive and ancillary services, not for margins on drugs. The care management fee supports services that are not typically compensated, including medication therapy management, patient education, psychologic assessment, team conferences, and financial and social work assistance (Sidebars A and B).

To incent participation in the oncology medical home program, the plan incorporated a 33% increase in drug margins by using ASP+12% as the allowed amount rather than the current ASP+10% commercial fee schedule. If a practice's true acquisition cost is ASP+4%, then margins for purposes of calculating CM fees increase to 8% from 6%, or a 33% increase.

### Payments: Shared Savings

A primary goal of the OMH project is to reduce avoidable ED visits and inpatient (IP) care and, in turn, reduce per capita cost. Priority Health and the practices will share any savings achieved if there is a statistically significant reduction in these 2 measures. The payout is on an annual basis. The plan provides baseline ED and hospitalization rates and interim utilization reports without financials to physician practices for tracking purposes.

Shared savings are not predicated on reducing drug costs or the total cost of

care. However, shared savings do require compliance with the preferred cancer regimens. If practices are at least 90% average compliant with National Comprehensive Cancer Network (NCCN) or 80% average compliant with practice-developed preferred regimens for 4 selected tumor types, savings are shared 50:50. In contrast, if practices are only 70% compliant with NCCN or 60% compliant with practice-developed preferred regimens, then practices receive only 20% of the net savings.

### Payments: Infrastructure

A critical element of the medical home is the development of clinical information systems with decision support, which can include electronic health records, electronic medical records (EMRs), patient registries, embedded practice guidelines, electronic care alerts and opportunities, and other decision-support tools. The infrastructure for managing patients' plans of care incorporates systems for registering, tracking, measuring, and improving essential coordinated services for high-risk patients. Although all practices are eligible for federal funding for EMRs through the Health Information Technology for Economic and Clinical Health Act, these dollars are only available retroactively. Restructuring the care delivery systems within a practice requires intellectual, time, and financial resources. In recognition of the efforts required to transform a practice, the plan agreed to pay a \$1500 per year per physician infrastructure payment support for the first 2 years of the program.

### Payments: Enhanced Services

**Tele-visits and e-visits.** Not all health services require face-to-face visits. Priority Health allows the use of syn-

chronous visits (tele-visits) or asynchronous visits (e-visits) when physical examination is not required. This reimbursement provides an alternative to the payment rule that precludes an evaluation and management service and chemotherapy infusion service on the same day. Reimbursement for alternate visit types is consistent with primary care medical home initiatives.

**Treatment planning.** Two new treatment planning codes (S0353 and S0354) allow physicians to be compensated for treatment planning and care coordination both for initial treatment and with a change of regimen. These codes are similar to those used by radiation oncologists planning radiation treatment. The use of these codes is not well defined. For the purposes of the OMH program, the plan and practices have agreed to the following criteria:

1. Diagnosis including histology, stage, and relevant biomarkers
2. Current performance status (Eastern Cooperative Oncology Group [ECOG], Karnofsky, or other)
3. Prognosis and goal/intent of therapy
4. Chemotherapy regimen, dosing and frequency, and planned number of cycles
5. A patient treatment plan to include criteria 1 through 4 and written side effect and management information, cancer-related resources, and key practice contacts and their role in the patient's care

Reimbursement for other services including E&M codes, drug administration codes, and laboratory and imaging services is unchanged and paid according to the health plan fee schedule. Dispensing of oral drugs is permissible within the program; these drugs are subject to the preferred regimens

## Sidebar B. Calculation of Care Management Fee

The monthly care management fee is calculated by dividing the participating practices' baseline net margins on drugs by the calendar months in which patients received active oral or IV chemotherapy. Members receiving oral and IV chemotherapy simultaneously are only eligible for 1 care management fee per month.

1. All medical drug claims for oncology drugs (CPT-4 codes, J-codes, C-codes) from the tax ID or IDs of the practice(s) are identified for the agreed-upon 12-month time period preceding the demonstration project initiation.
2. The net margin is defined as the difference between the average acquisition cost and the plan's fee schedule. The net margin is calculated for each patient and each product and then summed to yield the product-specific net margin.
3. Active chemotherapy months are calculated by merging pharmacy and medical claims databases and identifying patients with a cancer diagnosis who received an active chemotherapeutic treatment during that month.
4. Product-specific care management fees are then calculated as the net drug margin during a 12-month period divided by the total number of chemotherapy months.



**Table 1. Selection of Preferred Regimens: Non-Small Cell Lung Cancer**

Non-Small Cell Lung			
Adjuvant	Squamous	Non-Squamous	EGFR Mutated
A	Cisplatin/Gemzar	Cisplatin/Alimta	N/A
B	Carbo/Taxol	Cisplatin/Alimta	N/A
C	Platinum/Navelbine or Platinum/Taxotere	Platinum/Navelbine or Platinum/Taxotere	N/A
D	Cisplatin/Gemzar	Cisplatin/Alimta	N/A
1st Line Metastatic	Squamous	Non-Squamous	EGFR Mutated
A	Carbo/Gemzar	Carbo/Tazol/Avastin	Tarceva
B	Carbo/Taxol	Carbo/Tazol/Avastin	Tarceva
C	Carbo/Taxol or Taxotere/Gemzar		Tarceva
D	Carbo/Alimta/Avastin	Carbo/Alimta/Avastin	Tarceva
2nd Line Metastatic	Squamous	Non-Squamous	EGFR Mutated
A	Taxore	Alimta	Carbo/Alimta
B	Gemzar	Alimta	Alimta
C	Taxotere or Erlotinib	Carbo/Alimta	Alimta
D	Taxore	Taxore	Alimta

N/A indicates not available.

previously described. Copays, coinsurance, deductibles, and out-of-pocket maximums for patients remain in effect; these do not apply to the patient case management fee or to ACP.

**Care Delivery Redesign**

The second key element of the OMH program is care delivery redesign. As part of the OMH program, Priority Health and the practices agreed to collaborate on care delivery redesign in 4 domains, including use of preferred regimens, care management, ACP, and survivorship. All parties agreed to focus on survivorship at a later date.

**Preferred Regimens**

While many pathways programs implemented by third parties are based on state or regional consensus, they remain unnecessarily broad and lack input from individual oncologists and practices. In the OMH program, the plan and the practices mutually agreed to resolve both of these issues by having oncology practices establish single “preferred regimens” for at least 4 high-volume conditions in the adjuvant and first- and second-line metastatic settings, where appropriate. The regimens must be consistent with the most recent version of the NCCN guidelines ([www.nccn.org](http://www.nccn.org)).

Incorporation of performance status, such as the ECOG performance status or Karnofsky score, serves as a critical data point for decision mak-

ing. It is relevant both for selecting the therapeutic options appropriate for an individual patient and for assessing whether or not chemotherapy should be given on a given day. In fact, the first ASCO Choosing Wisely quality improvement measure proposes avoiding unnecessary anticancer therapy, including chemotherapy, in patients with advanced solid-tumor cancers and a low performance status (3 or 4), and instead focusing on palliative and supportive care or clinical trials (<http://connection.asco.org/Magazine/Article/ID/3190/Choosing-Wisely-Constructing-a-Top-Five-List-in-Oncology.aspx>).

Early results demonstrate that practices can readily meet these requirements. Further, their selections of preferred regimens are very similar (Table 1), which is remarkable because the practices developed these regimens in-

dependent of each other and without external input.

At present, there is no automated means of collecting tumor type, stage, biomarker status, or performance status. All results are based on self report. Most practices have agreed to use an independent third party to collect and report results. The results from the first 2 months of the program are shown in Table 2. Overall, 97% of adjuvant, first-, or second-line therapies were consistent with the NCCN guidelines, while 86% of therapies were consistent with the practices’ self-selected preferred regimens.

**Care Management**

Proactive patient engagement and early intervention is critical to reducing potentially avoidable care and complications. Consultants in Medical Oncology and Hematology, PC, has demonstrated that effective triage and symptom management protocols can reduce ED visits per chemotherapy patient year by 65% and hospitalizations per chemotherapy patient year by 43%.<sup>6,7</sup> Furthermore, the vast majority of clinical calls (approximately 75%) can be managed at home when patients call early in their symptom course.

The Oncology Medical Home care management program is intended to improve patient care and outcomes by having a consistent expectation of patients and practices alike. For patients, the plan and the practices mutually agreed that setting patient expectations to call the practices first was critical to reducing side effects, ED visits, and hospital admissions and to improving time on therapy. Likewise, we agreed that proactive care management required patient education protocols related to expected medication side effects, and phone triage protocols to ensure consistency in response by the clinician. At minimum, specific target areas include chemotherapy-induced nausea and vomiting, dehydration, constipation & diarrhea, fever,

febrile neutropenia, depression, and fatigue.

Practices track their triage line call disposition with, at a minimum, the following categories: manage symptoms at home, office visit today, office visit tomorrow, referral to primary care or specialty care physician, referral to the ED, or direct admission to the hospital. Re-engineering practices to meet these requirements has taken more time and effort than anticipated. Many practices have adopted software applications such as Navigating Cancer for their patient education portal. Most practices are adapting the Oncology Nursing Society’s PEP program for incorporation in their EMRs.

*A more vexing problem has been the implementation of practicewide care redesign programs with support from only 1 payer.*

**ACP**

Both the practice and the health plan are committed to promoting evidence-based initiatives supporting the goals of improved patient experience, improved health outcomes, and reduced per capita costs. Peer-reviewed evidence shows that patients who participate in an ACP program have less fear and anxiety, have a better ability to influence and direct their medical care, believe that their physicians have a better understanding of their wishes, and have a greater understanding and comfort level with their illness than they had before ACP. Moreover, for patients who participate in ACP discussions there

**Table 2. Results from First 2 Months of the OMH Program**

	National Guidelines (Current Month)			National Guidelines (Year to Date)			Preferred Regimens (Current Month)			Preferred Regimens (Year to Date)		
	On	Total	%	On	Total	%	On	Total	%	On	Total	%
Overall Program Compliance	7	8	88%	30	31	97%	3	4	75%	12	14	85%
A	0	0	0%	8	8	100%	0	0	0%	5	5	100%
B	1	1	100%	8	8	100%	0	0	0%	2	2	100%
C	1	1	100%	9	9	100%	0	1	0%	2	4	50%
D	5	6	83%	5	6	85%	3	3	100%	3	3	100%

OMH indicates oncology medical home.

**Table 3. Performance Metrics in 4 Different Domains**

DOMAIN: Preferred regimens	Reporting party
% compliance with preferred regimen for first-and second-line chemotherapy	Practice
90% compliance with NCCN guidelines; others adjudicated with evidence of ACP	Practice
% of chemotherapy infusions administered in an office setting	Plan
DOMAIN: Care management	Reporting party
# of calls per symptom type with disposition (home, same-day visit, next-day visit, ED, direct admit)	Practice
ECOG performance status or Karnofsky score documented at each chemotherapy contact	Practice
Non-elective hospital admissions per 100 patient chemo months	Plan
ED visits per 100 patient chemo months	Plan
DOMAIN: Advance care planning	Reporting party
% of new patients with ACP discussions within 60 days of the first dose of chemotherapy	Plan
% of patients with an advanced directive in the medical record within 60 days of starting chemo	Practice
% of cancer patients admitted to the hospital last month	Plan
% of patients prescribed chemotherapy in last 2 weeks of life	Plan
% enrolled in hospice within 3 days of death	Plan
DOMAIN: Patient satisfaction and experience	Reporting party
Regular patient experience and satisfaction survey from the Community Oncology Alliance ( <a href="http://www.communityoncology.org">www.communityoncology.org</a> )	Practice

ACP indicates advance care planning; ECOG, Eastern Cooperative Oncology Group; ED, emergency department; NCCN, National Comprehensive Cancer Network.

are fewer associated resuscitations, fewer intubations, fewer ICU days, better quality of life, earlier referrals to hospice, and less depression.<sup>8</sup> Among caregivers, there is a better quality of life, less depression, and less bereavement when end-of-life issues are discussed.<sup>9</sup> Patients with advanced cancer who reported having EOL conversations with physicians had significantly lower healthcare costs in their final week of life. Higher costs were associated with worse quality of death.<sup>10</sup>

Both ASCO and the NCCN Palliative Care Guideline (V2.2012) integrate ACP. For example, the latter states that providers should “elicit personal values and preferences for end of life care and congruence with values and preferences of family and health care team... (and) encourage the patient to discuss goals and preferences with family, provide advanced directives, and designate healthcare proxy.” Health insurers are required to have shared decision-making programs in place under Section 936 of the Patient Protection and Affordable Care Act (PPACA). Shared

decision making requires collaborative processes between clinicians and patients, caregivers, or authorized representatives. ACP is, by definition, a shared decision-making process that provides patients and families with information about trade-offs among treatment options and facilitates the incorporation of patient preferences and values into the medical care plan.

By mutual agreement between the physician practices and the plan, the former must establish an ACP program for patients receiving chemotherapy. At a minimum this must include a facilitated discussion with patients receiving treatment for metastatic disease within 60 days of initiation of chemotherapy and prior to additional treatment for disease progression. The facilitated discussion is typically with a trained staff member—not necessarily with the physician—and the patient and family members. When ACP documents are completed, the program requires insertion into the chart and filing with the patient’s preferred hospital.

The optimal timing for these discussions is not known. The timing requirement for this program is arbitrarily arrived at based on the assumptions that 1) the majority of people would expect at least 1 trial of therapy, 2) introduction at the initial visits would create confusion, and 3) most patients would not progress within the first 60 days. However, it is known that goals and preferences for care change with cancer patients, thus the need for follow-up discussions each time the patient’s disease progresses.

Each practice is allowed to design or select a program most suitable to the practice. One practice has chosen to implement the *Respecting Choices* program from Gunderson Lutheran Foundation ([www.gundluth.org/foundation](http://www.gundluth.org/foundation)) while other practices have adopted the *Five Wishes* program ([www.agingwithdignity.org](http://www.agingwithdignity.org)). In either case, practices have had to design a replicable process for ensuring that patients can have a facilitated discussion at the relevant time. All practices have chosen to have a scripted introduction, indicating that these discussions occur with all patients in the practice who have incurable disease. Other logistical issues that need to be resolved are who will introduce the topic, how the appointment is to be scheduled, where consultations will occur (home or office), and how to bill for the services.

Most experience to date has been with the initial discussion. In fewer than 10% of cases do patients decline the discussion outright, while approximately 25% of patients indicate that they’ve already had a discussion or have an advance directive. In these circumstances, strategies need to be de-

veloped for engaging patients and their families in a review of their goals and preference for care to assist the practice in knowing and respecting their choices. For patients and families who have gone through the process, over 90% have welcomed the discussions and found them helpful in sharing be-

liefs and preferences. In fact, in one practice, the availability of a trained social worker and psychologist has led to more referrals of existing patients by oncology infusion nurses than of new patients. Many challenges have surfaced. Typically these conversations take 1 to 2 hours, yet reimbursement is not available from most insurers. Priority Health has begun to reimburse any licensed healthcare provider for discussion facilitation using S0257, counseling and discussion regarding advance directives or end of life care planning and decisions, with patient and/or surrogate. Documentation for reimbursement minimally includes 1) the person designated to make decisions for the patient if the patient cannot speak for him- or herself, 2) the types of medical care preferred, and 3) the comfort level that is preferred. This code can also be used for POLST documentation.

At present, coverage is only for fully insured and self-insured patients, although the plan is actively exploring how to cover these services for Medicare and Medicaid recipients. Although the ACA only requires that the plan cover these services as preventive services when recommended by the US Preventive Services Task Force, they are covered by the plan at no cost to the patient based on national recommendations from the American College of Physicians and the American Medical Association, independent of age or health status.

#### Oncology Medical Home Performance Metrics

The third key element in the OMH initiative centers is codevelopment of

## Provider-payer partnerships are necessary to evaluate experimental payment models that create greater provider accountability for Triple Aim outcomes of patient experience, individual and population health outcomes, and per capita cost.

performance metrics in 4 different domains. A fifth domain on survivorship will be added later. The initial metrics and the party responsible for the measurement are outlined in **Table 3**. Of the 4 domains, the most challenging has been the ACP domain, primarily because getting accurate date-of-

performance metrics in 4 different domains. A fifth domain on survivorship will be added later. The initial metrics and the party responsible for the measurement are outlined in **Table 3**.

Of the 4 domains, the most challenging has been the ACP domain, primarily because getting accurate date-of-

death data is a challenge. Measures of admission and chemotherapy during the last weeks of life as well as hospice in the last 3 days of life are all dependent on accurate date-of-death data. While practices could secure this information, the preferred alternative is to match the health plan cancer registry to the State of Michigan Vital Records death index. A probabilistic linkage to the national death index is also a viable albeit more expensive option.

Another significant measurement challenge has been tracking phone triage disposition to assess the impact of enhanced patient education and nursing triage protocols. Capturing triage disposition in most EMRs is difficult, requiring either inefficient manual tallies, electronic tools independent of the EMR, or expensive revisions to EMR software.

### Implementation Challenges

Beyond the implementation challenges noted previously, 2 others bear mention. Reconciliation of the care management fees has been a time-consuming effort. The plan pays the fee prospectively based on an estimated number of patients and reconciles within 120 days. Since the practice does not bill the plan, reconciling actual versus anticipated payments has required clarification of the eligibility rules. Most commonly, patients are ineligible for payment because they did not receive chemotherapy during a given month due to chemotherapy delays or, less commonly, hospitalization.

Priority Health pays the case management fee without requiring the practice to bill the plan. While this relieves the practice of having to bill the plan, many health plans are precluded from paying for non-claims-based services without prior approval from the employer. In 2013, new CPT-4 codes provide a mechanism for paying complex chronic care coordination services (99487-99489). This circumvents the challenges of non-claims-based reimbursement but does require practices to actively bill care management fees.

A more vexing problem has been the implementation of practicewide care redesign programs with support from only 1 payer. The preferred regimen component of the program is mutually compatible with major pathways programs within the state of Michigan. While the enhanced care processes are typically available to all patients, the enhanced reimbursement is available only from a single payer at this time. (Medicare remains the largest single payer for most practices; in most prac-

tices the Priority Health market share is 5% or less.)

The Michigan Society of Hematology and Oncology (MSHO), representing Michigan oncologists, and the Community Oncology Alliance (COA), representing community oncologists, are working with all Michigan payers on a statewide oncology medical home/neighborhood proposal that would form the basis of an all-payer strategy. Payers met in November 2012 and reached consensus on the following points:

1. Payers are committed to finding alternative ways to pay for oncology care;
2. Payers have to find a way to assess quality of oncology care and reward it;
3. Use of the medical home model has transformed care;
4. There is synergy between the OMH and drug pathways; in fact, they are complementary;
5. Incorporation of advance care planning is an essential component of any transformation; and
6. Collaboration among payers can hasten the pace of change; lack of it can drive change in the provider community to a halt.

Finally, bridging the gap between desired state and current state takes resources that practices don't have or can't make available. To bridge that gap, some practices have partnered with external resources such as Physician Resource Management, Ion Solutions, COA, and MSHO to effect systems and process changes.

### Limitations

The care management and performance elements of the OMH model can be applied to any oncology practice. While the OMH model of payment reform and care management redesign works especially well with self-employed community practices, the model is less appealing for employed practices, especially those affiliated with 340(b) facilities that are unlikely to agree to drug reimbursement at acquisition costs. Nevertheless, engaging employed physicians in efforts to improve cancer care quality, value, and health outcomes is critical to raising the communitywide standard of care.

A second limitation is the applicability of this model to practices where government payments form a substantial portion of the practice's income. While a number of mechanisms exist for enhancing payment to providers, lack of applicability to Medicare and Medicaid recipients further fragments a challenging and complicated reim-

bursement web, creating misaligned incentives for patient care.

### Summary

The Oncology Medical Home program demonstrates an effective working model for restructuring cancer payments and care. It complements and in fact takes oncology pathways programs to a new level through creation of practice-specific preferred regimens. It eliminates practices' financial dependence on drug margins and reduces the current misalignment between cancer payments and cancer outcomes by taking a patient-centric approach. Further, it enhances practice payments for cognitive services provided by the oncology team and rewards teams for improving patient care and reducing avoidable ED visits and inpatient care. Provider-payer partnerships are necessary to evaluate experimental payment models that create greater provider accountability for Triple Aim outcomes of patient experience, individual and population health outcomes, and per capita cost. **EBO**

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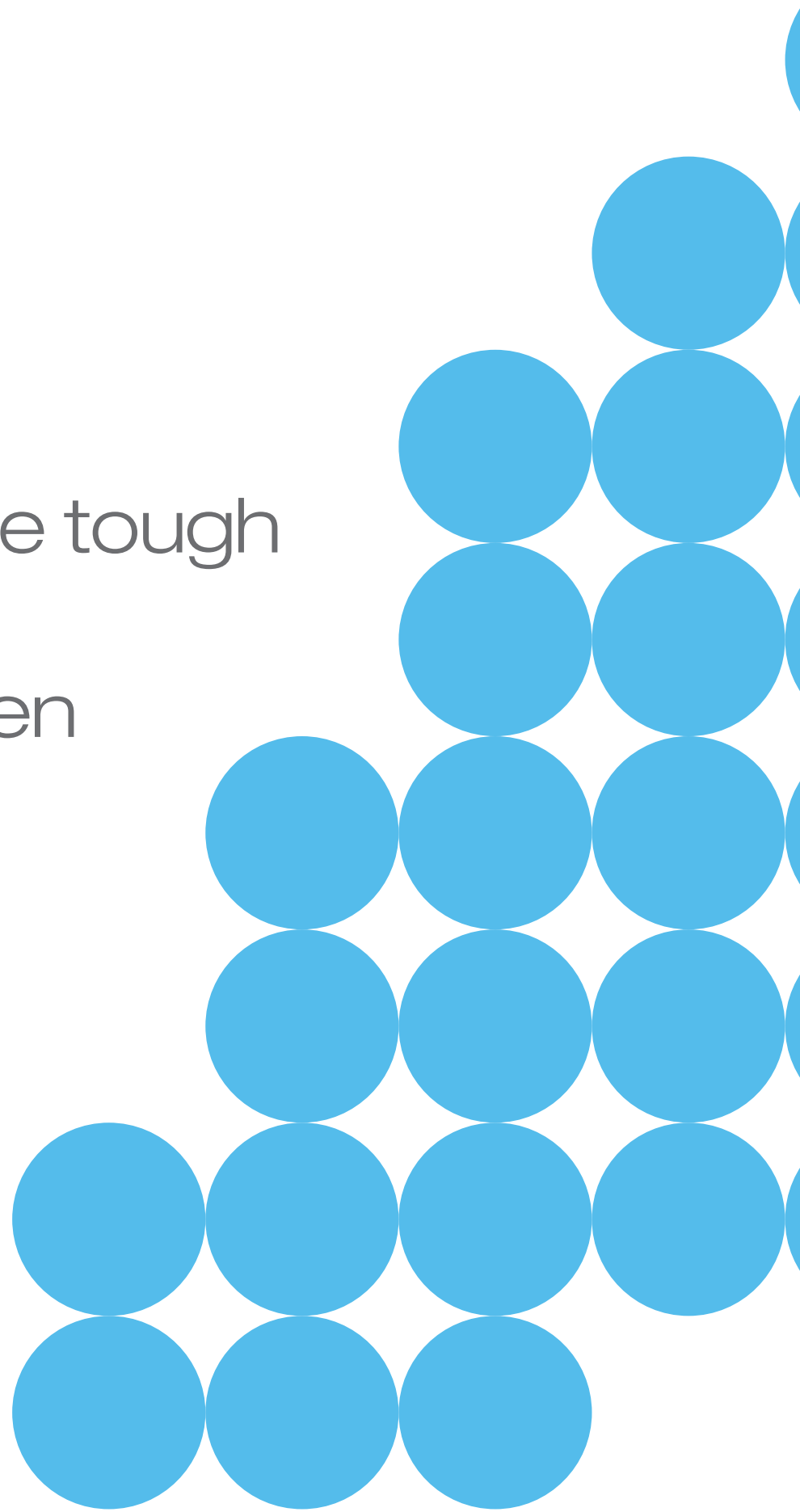
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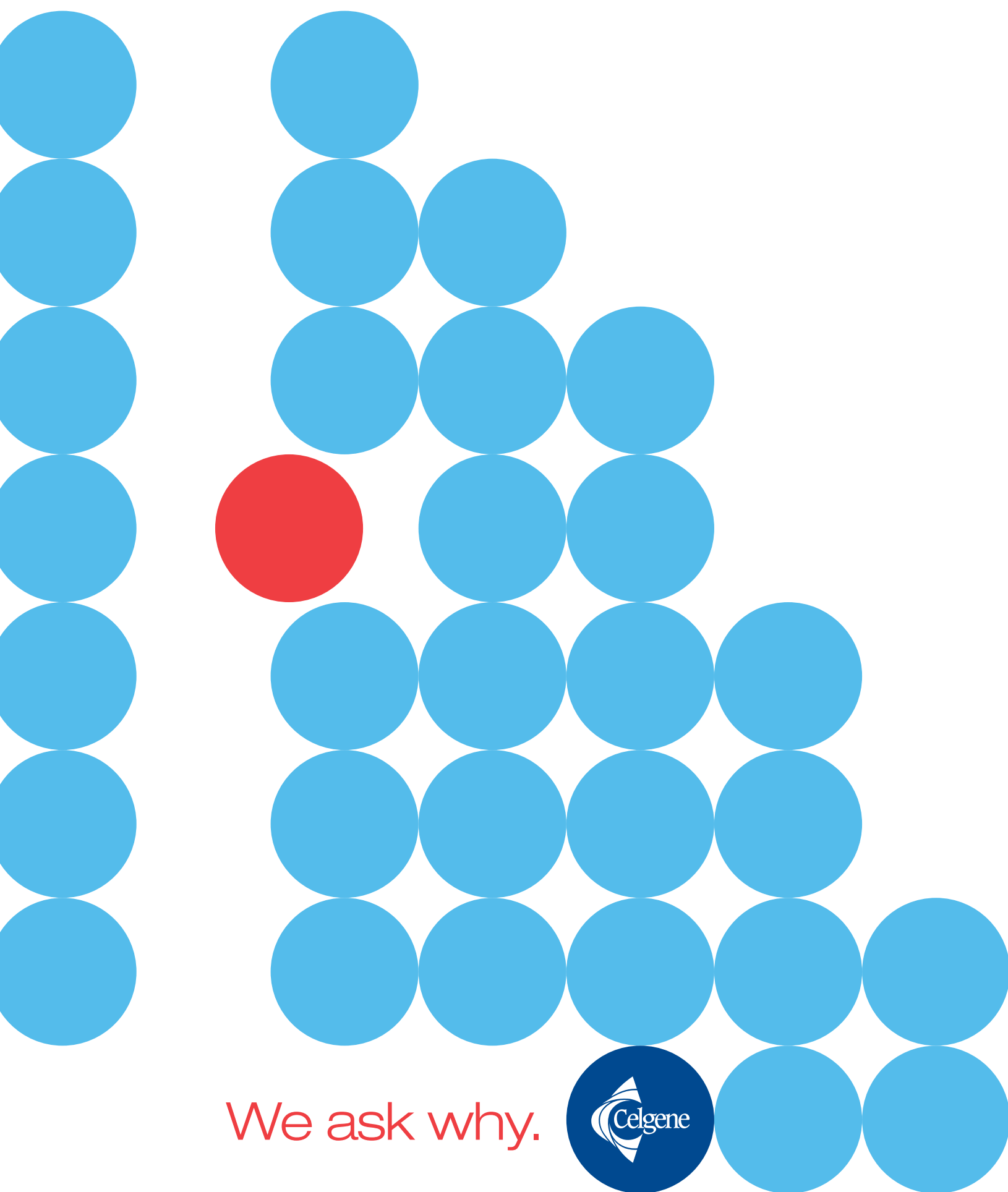
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All lung cancers are tough  
to treat.

Why are some even  
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## CHRONIC MYELOID LEUKEMIA

## Trying to Calculate the Economic Value of Dasatinib or Nilotinib for Imatinib-Resistant CML

Although it is now standard practice to utilize the second-generation tyrosine-kinase inhibitors dasatinib or nilotinib in patients whose chronic myeloid leukemia has recurred while taking imatinib treatment, published support for the economic value of this approach is lacking. Investigators from the University of Exeter, United Kingdom, conducted a review of the literature and produced an economic model to help fill this information gap.

They evaluated contributions to key databases (MEDLINE [including MEDLINE In-Process and Other Non-Indexed Citations], EMBASE [ISI Web of Science], Conference Proceedings Citation Index, as well as 4 other sites). Their research led to 15 relevant studies, the most recent from June 2009.

Two separate decision-analysis economic models for chronic myeloid leukemia (CML) were utilized, in which patients in chronic-phase CML either showed the potential to become or did become resistant to a normal dose of imatinib (imatinib resistant), or due to adverse events had to cease imatinib treatment (imatinib intolerant). Another was used to evaluate patients with CML that had progressed to blast crisis.

Although the number of studies regarding the effectiveness of dasatinib and nilotinib for treating chronic-phase CML patients (who were either imatinib resistant or imatinib intolerant) was limited, the investigators found ample evidence for the clinical effectiveness of

these agents, based on positive cytogenetic and hematological responses.

However, it was very difficult, they stated, to come to any conclusions regarding cost-effectiveness with either dasatinib or nilotinib treatment of patients in those with imatinib-resistant CML. Serious data flaws were noted, in one way or another, for all the economic models produced.

**Although the second-generation TKIs appear to add clinical value to the armamentarium against CML, the clinicians acknowledge that a meaningful cost-effectiveness conclusion is not possible.**

All available data regarding accelerated and blast crisis came from observa-

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Harry Erba, MD, PhD, notes that molecular monitoring in patients with CML allows the physician to assess the bone marrow in a non-invasive way once the tumor has entered into complete cytogenetic remission (<http://bit.ly/U2pVrk>)



tional single-arm trials. Unfortunately, meaningful comparisons between the treatments was greatly undercut because of various and possible baseline characteristic variations.

Accelerated phase and blast crisis de novo models could not be expanded because the available clinical data were deficient. In addition, there was sparse evidence regarding the effectiveness of second-generation tyrosine-kinase inhibitors (TKIs) compared with high-dose treatment with imatinib, which severely weakened the economic evaluations done by the manufacturers.

Interestingly, a separate review of the studies on the value of high-dose imatinib in patients with chronic-phase CML resistant to standard-dose imatinib revealed that up to one-third experienced a complete cytogenetic response (up to four-fifths experienced a complete hematologic response), with grade 3 or 4 adverse events occurring in 40% of patients (up to one-fifth discontinued because of these adverse effects). In an economic analysis, nilotinib appeared to have greater cost-effectiveness than high-dose imatinib, followed by dasat-

ininib, in these resistant patients. However, they caution that the study was not based on direct comparisons with identical outcomes measures.

Although the second-generation TKIs appear to add clinical value to the armamentarium against CML, the clinicians acknowledge that a meaningful cost-effectiveness conclusion is not possible. Until a randomized, 3-way, double-blind clinical study involving dasatinib, nilotinib, and high-dose imatinib is conducted, they added, the true economic value of the second-generation TKIs cannot be revealed. **EBO**

Sources: Rogers G, Hoyle M, Thompson Coon J, et al. Dasatinib and nilotinib for imatinib-resistant or -intolerant chronic myeloid leukaemia: a systematic review and economic evaluation. *Health Technol Assess.* 2012;16(22):1-410.

Loveman E, Cooper K, Bryant J, et al. Dasatinib, high-dose imatinib, and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: a systematic review and economic evaluation. *Health Technol Assess.* 2012;16(23):iii-xiii, 1-137.

## Chronic Myeloid Leukemia Treatment Practices in the United States

The multinational, prospective WORLD CML registry was established in order to measure how patients with CML are managed by evaluating global clinical practice patterns. This registry, with sites around the world, recently examined results for patients with CML at locations in the United States and assessed how practice patterns correspond with National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines.

The care of 377 patients (median age, 53 years; range, 18-91 years) with a confirmed CML diagnosis enrolled in the United States from February 2008 to December 31, 2010, was analyzed by American researchers. Of these participants, 363 (96%) received a chronic phase diagnosis.

First-line therapy of imatinib was prescribed for 73% of patients with chronic phase CML, compared with hydroxyurea

(6%), nilotinib (3%), and dasatinib (1%). (The clinicians noted that patients may have received more than 1 medication.)

The median treatment period lasted 7.6 months (range, 0.1-33.5 months).

The dose of imatinib treatment was

**Table 1. Type of Disease Assessments in Patients With Chronic-Phase CML Treated With First-Line Imatinib**

	Time Since Start of Imatinib <sup>a,b</sup>					
	3 mo (N = 265)	6 mo (N = 233)	12 mo (N = 193)	18 mo (N = 135)	2 y (N = 92)	3 y (N = 18)
Patients with assessment	49%	74%	85%	79%	89%	78%
Hematologic	45%	68%	76%	67%	82%	72%
Cytogenetic <sup>c</sup>	13%	34%	32%	25%	28%	33%
Molecular	16%	43%	51%	47%	64%	50%

<sup>a</sup>N values correspond to the number of patients still in the registry at each time point.  
<sup>b</sup>Includes assessments within the following ranges: 3 mo, start of first-line therapy to 4.5 mo; 6 mo, >4.5-9 mo; 12 mo, >9-15 mo; 18 mo, >15-21 mo; 2 y, >21-30 mo; 3 y, >30-42 mo.  
<sup>c</sup>Includes fluorescence in situ hybridization.

**Table 2. Monitoring Guidelines From the National Comprehensive Cancer Network**

Test	Recommendation
<b>Bone marrow cytogenetics</b>	At diagnosis to establish the disease phase. If collection of bone marrow is not feasible. FISH on a peripheral blood specimen using dual probes for the <i>BCR</i> and <i>ABL</i> genes is an acceptable method of confirming the diagnosis of CML. At 3 months from initiation of therapy, if QPCR using International Scale (IS) is not available. At 12 months from initiation of therapy, if there is not CCyR or MMR. At 18 months from initiation of therapy, if not in MMR and lack of CCyR at 12 months. Rising levels of <i>BCR-ABL</i> transcript (1-log increase) without an MMR.
<b>Quantitative RT-PCR (QPCR)</b>	At diagnosis to establish baseline <i>BCR-ABL</i> transcript level. Every 3 months when a patient is responding to treatment. After CCyR has been achieved, every 3 months for 3 years and every 3-6 months thereafter. If there is a rising level of <i>BCR-ABL</i> transcript (1-log increase) with an MMR, QPCR analysis should be repeated in 1-3 months.
<b>BCR-ABL kinase domain mutation analysis</b>	<ul style="list-style-type: none"> <li>Chronic phase                             <ul style="list-style-type: none"> <li>For patients with inadequate initial response (failure to achieve PCyR or <i>BCR-ABL/ABL</i> ≤10% (IS) at 3 months or CCyR at 12 and 18 months.</li> <li>Any sign of loss of response (defined as hematologic or cytogenetic relapse or 1-log increase in <i>BCR-ABL</i> transcript levels and loss of MMR).</li> </ul> </li> <li>Disease progression to accelerated or blast phase.</li> </ul>

Source: Reprinted with permission from Hughes T, Deininger M, Hochhaus A. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting *BCR-ABL* transcripts and kinase domain mutations and for expressing results. *Blood*. 2006;108(1):28-37.

increased in 29 of the 363 patients with chronic phase CML (8%) primarily as a result of physician request and lack of efficacy. In 32 patients (9%), the imatinib dose was reduced, primarily because of

adverse events and physician request. Lack of efficacy and adverse events led to the treatment regimen being changed from imatinib to nilotinib in 21 patients (6%) and to dasatinib in 20 patients (6%).

Clinicians most commonly used hematology assessments to evaluate CML treatment progress (Table 1). After 3 months of imatinib treatment, a molecular assessment was sought for only

16% of patients, although up to 64% of patients underwent molecular disease testing by 2 years of therapy. The least common assessment, cytogenetics, was performed in only 13% of patients after 3 months and up to 34% after 6 months of treatment.

The investigators concluded that many patients being treated with first-line imatinib for chronic phase CML did not routinely undergo cytogenetic or molecular assessments. According to NCCN guidelines, such testing should be conducted more frequently (Table 2). They indicate that access to molecular testing may have been an issue during the study period, and that these findings therefore should be updated to reflect more current availability of cytogenetic and molecular testing. **EBO**

Source: Hermann R, Miller CB, Catchatourian R, et al. Understanding US treatment practices for the management of chronic myeloid leukemia (CML) in clinical practice: a US subgroup analysis of the WORLD CML Registry. Presented at the 54th annual meeting of the American Society of Hematology, Atlanta, December 8-11, 2012.

## Unfavorable Results of Imatinib Treatment in Patients With High *BCR-ABL* Levels

With several TKIs available today to treat patients whose CML has recurred despite standard imatinib therapy, it may be beneficial to predetermine in some way those patients who may be optimally treated with alternative agents. This points to the need for a better understanding of the relevant biomarkers to predict who will not respond sufficiently to imatinib treatment.

Recent reports have suggested that after 3 months of treatment with imatinib, patients with CML may experience inferior outcomes (in terms of both progression-free survival and overall survival [OS]) when they experience *BCR-ABL/ABL*<sup>IS</sup> levels above 10%, or more than 1% after 6 months of imatinib therapy. Italian and German researchers have attempted to extend this finding by 1 step: to determine whether high levels of *BCR-ABL* transcripts found at the time of diagnosis would also be connected with an inadequate reaction to imatinib treatment.

The researchers analyzed *BCR-ABL* levels of 230 patients with newly diagnosed CML who were to receive imatinib 400 mg/day. Either *ABL* or glucuronidase-beta (*GUS*) was used as reference genes for all molecular verifications.

The median follow-up time in the study population was 42 months. Cumulative incidences estimated at 5 years for complete hematologic responses, complete cytogenetic response (CCyR), and major molecular response were 98%, 89%, and 65%, respectively. Overall survival rate using 5-year probabilities was 93.8%, while a transformation-free survival rate, defined as survival without disease transformation to the accelerated phase or blast crisis, and failure-free survival (survival without imatinib failure as indicated in the 2009 European Leukemia Net recommendations) were 98% and 76%, respectively.

When *GUS* was used instead of *ABL* as a reference gene at diagnosis, connections between high *BCR-ABL* transcripts and the differential in inadequate IM responses were much greater. Both elevated *BCR-ABL/GUS*<sup>IS</sup> ( $P < .0001$ ) and elevated *BCR-ABL/ABL*<sup>IS</sup> ( $P < .0001$ ) levels were associated with a lower probability of optimal response. The investigators also indicated that after 12 months of imatinib therapy, a link existed between lower rates of cytogenetic response and higher *BCR-ABL/GUS*<sup>IS</sup> measurements ( $P < .0001$ ) but not higher *BCR-ABL/ABL*<sup>IS</sup> values ( $P = .18$ ).

They noted that overall survival could not be predicted by levels of *BCR-ABL/*

*GUS*<sup>IS</sup> or *BCR-ABL/ABL*<sup>IS</sup> at diagnosis. However, a more accurate connection

**This points to the need for a better understanding of the relevant biomarkers to predict who will not respond sufficiently to imatinib treatment.**

between high levels of *BCR-ABL/GUS*<sup>IS</sup> and lower probabilities of failure-free survival ( $P < .0001$ ) and transformation-free survival ( $P = .01$ ) was found when compared with high levels of *BCR-ABL/ABL*<sup>IS</sup> ( $P = .02$  and  $P = .36$ , respectively).

After subdividing the patient cohort into optimal responders, suboptimal responders, and subjects failing first-line therapy, based on the 2009 European

Leukemia Net criteria, the authors discovered that elevated *BCR-ABL/GUS*<sup>IS</sup> ( $P < .0001$ ) was a better determinant of patient outcome than elevated *BCR-ABL/ABL*<sup>IS</sup> ( $P < .004$ ). In addition, at diagnosis, the number of *BCR-ABL/GUS*<sup>IS</sup> transcripts was significantly different between the 3 patient groups (optimal vs suboptimal responses,  $P = .0002$ ; optimal vs resistant responses,  $P < .0001$ ; suboptimal vs resistant responses,  $P < .0001$ ). At the time of diagnosis, *BCR-ABL/ABL*<sup>IS</sup> levels only discriminated optimal from resistant responders ( $P = .005$ ). The researchers determined the threshold distinguishing those at low risk from patients at high risk as 16% *BCR-ABL/GUS*<sup>IS</sup> at diagnosis.

Patients with CML who would probably not benefit from imatinib treatment can be identified by high *BCR-ABL* transcripts when diagnosed, using *GUS* as a reference gene, the researchers concluded, and therefore should be given other TKIs as first-line treatment. **EBO**

Source: Vigneri PG, Stagno F, Stella AS, et al. High *BCR-ABL* levels at diagnosis are associated with unfavorable responses to imatinib mesylate. Presented at the 54th annual meeting of the American Society of Hematology, Atlanta, December 8-11, 2012.

## Payer Perspective

## Will Cytogenetic Testing Improve Value in CML Care?

Maria Lopes, MD, MS



As demonstrated in the presentation by Hermann and colleagues at the December 2012 American Society of Hematology meeting,<sup>1</sup> it is clear that in practice, cytogenetic testing in patients with CML is not performed according to the latest NCCN guidelines, which now call for an evaluation at 3, 12, and 18 months to assess cytogenetic response. This affords the opportunity to assess whether the choice of therapy is effective, and if not, to evaluate patient compliance, drug-drug interactions, or mutations that may render current treatment ineffective. Given the guidelines, it would seem appropriate for testing to be a standard of care, and yet variability in testing

still exists. At least 2 major issues may help explain why cytogenetic testing is not following NCCN recommendations.

One reason may be that although the NCCN guidelines call for cytogenetic testing at certain milestones, they do not sufficiently inform the decision-making process and recommend assessment and choice in second-line TKIs. For instance, once cytogenetic testing is done and resistance is apparent (in the form of mutations like T315I), it is unclear how to incorporate this information into a treatment decision and whether current therapy should be discontinued simply based on lab test results. It is also unclear whether a change in treatment ultimately affects overall survival and health outcomes. Furthermore, how does this influence what payers do to minimize waste and at what point should a payer require prescribers to change treatments that may be ineffective? How will testing impact shared decision making for patients of a specified age range, with comorbidities, specific mutations, and other considerations? As new therapies emerge that may induce fewer mutations or are the only agents that work in specific mutations, including T315I, this may become a more important consideration that minimizes waste and brings clinical utility to testing.

Second, NCCN guidelines do not factor cost into the treatment consideration. In other words, the guidelines are suggestive but are not sufficiently prescriptive for providers or payers to take action based on the results of cytogenetic testing. The updated guidelines offer a step in possibly identifying drug resistance and ineffective therapy, but new therapy options need to be incorporated for a more personalized approach to second-line therapy, defining which mutation is causing the resistance and which second-line treatment is appropriate to reduce waste and improve survival.

On a more practical level, the actual cytogenetic testing report may not always be easy to interpret, which leads to further ambiguity on how it should be incorporated into decision making. Payers, providers, and members need decision support tools to assist with patient assessment, compliance and adherence, and education on the clinical utility of cytogenetic testing, its implications for treatment considerations, and a framework for addressing the test results.

Given this level of ambiguity, it may be challenging for managed care organizations alone to take action at this time to promote or encourage the use of cytogenetic testing. Clear guidance is needed from NCCN on the implications of the results for treatment decisions and selection of therapy, and the approach to treatment.

The opportunity now exists, based on NCCN's focus on cytogenetic testing, to discuss with providers ways to optimize value from the available TKIs. Payers worry about the cost of these agents and invite discussions on ways to mitigate waste and inappropriate use associated with ineffective treatment to ensure that these represent adequate value for the dollars being spent. This will become even more critical should the use of combination TKIs be incorporated into the CML guidelines. The increased costs will affect not only health plans and insurers, but patients and those bearing risk for total cost of care, such as accountable care organizations.

The concept of value in cancer care is gaining momentum among providers. In October 2012, executives from Memorial Sloan-Kettering Cancer Center wrote in the *New York Times* that they would not utilize an expensive colon cancer therapy because they did not believe it represented good value.<sup>2</sup> This is a highly significant statement from a cancer center of excellence. In the past, providers did not generally consider cost of treatment a priority issue. With the trend toward accountable care organizations and using global or bundled forms of payment, this view may now be more common from the provider side.

As with many diseases, we often find significant variation in treatment and in the approach to patient management. Often, variability adds to cost, poor patient outcomes, and inefficient use of medical and financial resources. Evidence-based guidelines can help reduce this variation, but are often broad and too complex to implement. In a recent article in *BMJ*, the authors noted "unnecessary treatment in America accounts for 10% to 30% of health care spending, or up to \$800 billion per year."<sup>3</sup> The US system can no longer sustain or afford such waste.

CML represents another example of where more can now be done to improve the dialogue between health plans, key opinion leaders, and community oncologists to formalize pathways, reduce unnecessary treatment variability, and maximize the value of treatments, particularly when it comes to combining TKIs. This is a cost benefit discussion that will be increasingly common among unusual partners.

*Dr Lopes is chief medical officer at CDMI in Newport, RI.*

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**NCCN guidelines do not factor cost into the treatment consideration. In other words, the guidelines are suggestive but are not sufficiently prescriptive for providers or payers to take action based on the results of cytogenetic testing.**





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## MELANOMA

## The Economic Value of Ipilimumab as a Second-Line Treatment in Patients With Advanced Melanoma

In early 2011, ipilimumab, an anti-CTLA-4 monoclonal antibody with anti-tumor activity, was approved by the US Food and Drug Administration (FDA) for the treatment of advanced melanoma. Ipilimumab was compared with the gp100 vaccine in a clinical trial and patients survived a median of 3.7 months longer than those receiving the vaccine. In another trial, ipilimumab with dacarbazine was compared with dacarbazine in previously untreated patients with advanced melanoma. The investigators found that combination therapy yielded higher survivals at 1, 2, and 3 years.

Ipilimumab is an expensive treatment that is associated with positive clinical outcomes. Researchers from the United States and United Kingdom (and from Bristol-Myers Squibb, the manufacturer of ipilimumab) sought to evaluate the cost-effectiveness of ipilimumab compared with best supportive care in previously treated patients with advanced (unresectable or metastatic) melanoma.

Progression-free and overall survival data were used from a phase III trial of ipilimumab to model stable disease, progression, and death. Clinical outcomes, quality of life, and healthcare utilization were included in the analyses. The Markov model considered only the direct costs in patients with an average age of 55 years having advanced melanoma. A discount rate of 3% was

utilized for both costs and outcomes.

Because no previous clinical trial with another therapy demonstrated a prolongation of survival, best supportive care was defined as disease management without active chemotherapy. The researchers acknowledged that this may provide a conservative cost benefit for ipilimumab, as most patients usually receive some type of chemotherapy that increases treatment costs of advanced melanoma. Both the incremental cost-effectiveness ratio (ICER) and incremental cost utility ratio (ICUR) were estimated in the model. They included direct costs associated with pharmaceuticals, clinical management, and costs associated with toxicity-related events (Table).

The model used ipilimumab clinical data from a trial comparing the agent with gp100, dacarbazine, interleukin-2, and temozolomide. Ipilimumab demonstrated benefits in both progression-free survival and overall survival.

Those in the ipilimumab group demonstrated a mean gain of 1.88 life-years and 1.14 quality-adjusted life-years (QALYs) compared with patients receiving basic supportive care. The drug costs were higher in the ipilimumab group. They estimated the incremental cost-effectiveness ratios to be \$78,000 per life-year gained and \$129,000 for the incremental cost per QALY gained.

Based on their sensitivity analysis, and assuming a willingness-to-pay threshold of \$113,000 per QALY, the re-

searchers estimated a 6% chance that ipilimumab would be considered cost-effective. However, if the threshold were raised to \$146,000/QALY, ipilimumab would be considered cost-effective in better than 95% of the scenarios.

The investigators explained that the differences between the ICER and ICUR were expected, owing to the definitions utilized for disease progression from stable disease to progressive disease in the model. Using the costs of alter-

native therapies that have no shown benefit in survival would increase the cost-effectiveness of ipilimumab, as this therapy has been proved to improve survival. **EBO**

Source: Barzey V, Atkins MB, Garrison LP, et al. Ipilimumab in 2nd line treatment of patients with advanced melanoma: a cost-effectiveness analysis. *J Med Econ.* 2013;16(2):202-212.

**Table. Costs Used in the Cost-Effectiveness Model**

Parameter	Value
Drug Costs	
• Ipilimumab cost per cycle	\$30,000
• Ipilimumab administration	\$504
• Weekly cost for third-line treatment	\$89
On-treatment disease management costs	
• Ipilimumab	\$822
• Best supportive care	\$1518
Off-treatment disease management costs	
• Ipilimumab	\$1518
• Best supportive care	\$1518
Estimated average treatment costs per toxicity	
• Costs varied by the respective toxicity	\$775-\$8563 <sup>a</sup>

<sup>a</sup>For example, an episode of anemia was assigned an average treatment cost of \$851, and fever was assigned a cost of \$3304.  
Source: Barzey V, Atkins MB, Garrison LP, et al. Ipilimumab in 2nd line treatment of patients with advanced melanoma: a cost-effectiveness analysis. *J Med Econ.* 2013;16(2):202-212.

## Combined BRAF and MEK Inhibition in Melanoma Improves Cytogenic Response

Vemurafenib is a valuable treatment in patients with advanced melanoma who have the BRAF V600E mutation. However, roughly half of patients treated with vemurafenib have progression-free survivals of about 7 months before melanoma activity recurs. An international group of researchers from multiple centers sought to determine if a combination of investigational BRAF and MEK inhibitors might produce a more durable response.

This investigation was part of a larger study that determined the pharmacokinetic activity, clinical activity, and safety of oral dabrafenib (a BRAF inhibitor) and trametinib (an MEK or MAPK-kinase inhibitor). The trial of interest

was an open-label, randomized, phase II trial that included 162 patients with advanced melanoma who were therapy-naïve or received no more than 1 chemotherapy regimen (excluding any prior treatment with BRAF or MEK inhibitors).

The patients were randomly assigned treatment with either 150 mg dabrafenib bid monotherapy (54 patients; median age, 50 years) or 150 mg dabrafenib bid plus 1 daily dose of trametinib 1 mg (combination 150/1 therapy) (54 patients; median age, 49 years) or 2 mg (combination 150/2 therapy) (54 patients; median age, 58 years). Each of the 3 study groups in this phase had similar poor prognostic attributes including brain metastases,

M1c disease, and high lactate dehydrogenase levels. The frequency of cutaneous squamous-cell carcinoma (including keratoacanthoma) was 19% for the dabrafenib monotherapy group, 2% for the combination 150/1, and 7% for the combination 150/2 group ( $P = .004$  and  $P = .09$ , respectively).

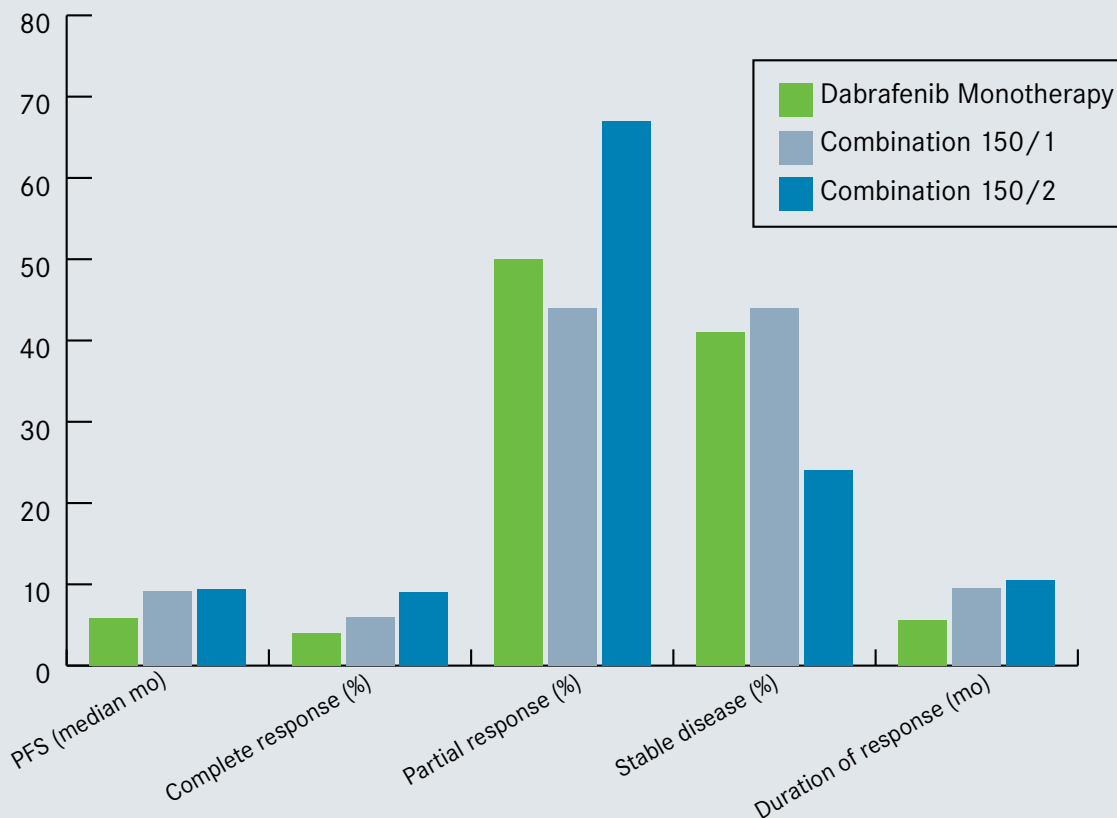
The median follow-up time was 14.1 months (range, 10.8-17.6 mo) at the time of the planned efficacy analysis. The researchers calculated progression-free survivals (PFSs) of 9.4 months for the combination 150/2 patients, 9.2 months for the combination 150/1 patients, and 5.8 months for monotherapy patients. An independent review committee assigned a hazard ratio for progression or death of 0.55 (95% confi-

dence interval, 0.33 to 0.93;  $P = .02$ ) for those receiving the 150/2 combination (Figure).

After 12 months, 41% of patients in the 150/2 group were still experiencing PFS compared with only 9% of monotherapy patients ( $P < .001$ ). When investigators stratified patients according to BRAF V600E mutation or V600K mutation, they did not find any difference in outcome.

Seventy-six percent of the patients in the combination 150/2 group experienced a complete or partial response compared with 54% in the monotherapy group (54%;  $P = .03$ ). The median overall survival rate, acknowledged the authors, could not be analyzed, because it had not yet been reached.

**Figure. Efficacy End Points for BRAF-MEK Inhibition in the Intention to Treat Population**



PFS indicates progression-free survival.

Source: Adapted from Flaherty KT, Infante JR, Daud D, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med.* 2012;367(18):1694-1703.

At 1 year, 79% of the patients in the 150/2 group and 70% in the monotherapy group were alive. When the disease progressed in patients currently receiving

monotherapy with the BRAF inhibitor, 80% crossed over to the 150/2 combination therapy group.

The side effect of rash was higher in

the monotherapy group (36%) versus the combination 150/1 and 150/2 populations (20% and 27%, respectively). However, the combination groups had

a more widespread MEK-inhibitor-associated acneiform dermatitis than the monotherapy subjects (11% for 150/1, 16% for 150/2, 4% for monotherapy treatments).

Adverse events that were seen more frequently in the combination 150/2 group were pyrexia (all grades, 71%) and chills (all grades, 58%). In addition, other adverse events that occurred more frequently in the combination 150/2 group than in the monotherapy patients were fatigue (53% of patients), nausea (44%), vomiting (40%), and diarrhea (36%).

The investigators conclude that this combination of BRAF-MEK inhibitors is at least partly successful in mitigating the resistance in advanced melanoma to BRAF inhibition alone that occurs over time. Dabrafenib and trametinib given to patients at their full single-agent doses proved to be safe and effective when combined, the clinicians stated. This trial, they concluded, supports the effectiveness of using a combination regimen of BRAF-MEK inhibitors for treating patients with advanced melanoma. **EBO**

Source: Flaherty KT, Infante JR, Daud D, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med.* 2012;367(18):1694-1703.

## The Effect of Ipilimumab on Health-Related Quality of Life in Patients With Unresectable Advanced Melanoma

Patients diagnosed with melanoma are typically affected psychologically. Treatment usually causes impaired physical functioning and fatigue. Researchers summarized health-related quality of life (HRQOL) during the 12-week ipilimumab induction period in previously treated patients diagnosed with advanced stage III or IV melanoma.

Patients in the study were randomized to receive 1 of 3 treatments: ipilimumab plus gp100 vaccine, gp100 vaccine plus placebo, or ipilimumab plus placebo. The European Organization of Research and Treatment of Cancer Quality of Life Questionnaire (EORT QLQ-C30) was utilized to assess HRQOL. This tool entails global health status, and physical, emotional, role, cognitive, and social functioning. Higher scores are indicative of better functioning. Differences in scores were subgrouped into 4 categories (eg, “no change” [0-5 points], “a little” [5-10 points], “moderate” [10-20 points],

**Therefore, the authors conclude that HRQOL changes should not be a concern for those patients with advanced melanoma and their physicians considering ipilimumab treatment.**

and “very much” [ $>20$  points]). A score differential of 0 to 10 points was interpreted as no or minimal impact on patient HRQOL.

The researchers reported that after 12 weeks, most patients reported that changes to HRQOL outcomes were no greater than minimal. The only statistically significant difference in score was for constipation, in a comparison of the ipilimumab plus gp100 and the gp100 alone groups. Scoring indicating “moderate” function and global health status score were role function in the ipilimumab alone group and role function and global health in the gp100 group. Symptom scoring rating a “moderate” were fatigue in the ipilimumab plus gp100 group; fatigue, sleep disturbances, and appetite loss in the ipilimumab alone group; and fatigue, pain, sleep disturbances, appetite loss, and constipation in the gp100 alone group.

Patients older than 65 years tended to have more “moderate” changes in health status than the patients young-

er than 65 years. The greatest differences, albeit moderate, were observed for role function, social function, global health, dyspnea, sleep disturbance, appetite loss, and diarrhea. It is difficult to fully appreciate the importance of the findings owing to the small sample size of the  $>65$  years group, as the mean age was 55.6 years to 57.4 years across all of the study groups.

Treatment within all 3 treatment groups resulted in minimal changes in HRQOL. Therefore, the authors conclude that HRQOL changes should not be a concern for those patients with advanced melanoma and their physicians considering ipilimumab treatment. **EBO**

Source: Revicki DA, van den Ertwegh AJM, Lorigan P, et al. Health related quality of life outcomes for unresectable stage III or IV melanoma patients receiving ipilimumab treatment. *Health Qual Life Outcomes.* 2012;10:66.

## Is Daily Sunscreen Use Cost-Effective for Preventing Skin Cancer?

Exposure to ultraviolet radiation is an important risk factor for the development of skin cancers. A major study previously demonstrated the benefit of sunscreen as an effective strategy, both clinically and economically, for reducing the burden of squamous-cell carcinoma. However, the study did not investigate the long-term benefit of using sunscreen to prevent melanoma, the least prevalent but more often fatal skin cancer.

To evaluate the economic effects of sunscreen use to prevent melanoma, investigators evaluated data from the Nambour Skin Cancer Prevention Trial conducted in Queensland, Australia, from 1992 to 2006. In this trial, the intervention group was encouraged to apply daily a sunscreen with an SPF rating of at least 15, which was provided free of charge at designated study clinics. The study group was instructed to apply the sunscreen daily to their head, neck, arms, and hands, and the control group was instructed to apply sunscreen at their discretion. The decision model

tracked multiple cohorts to examine the health and cost outcomes of participants with different profiles. Key measures included time since diagnosis, costs, number of melanomas, QALYs, and life-years lived.

All participants were melanoma free at the start of the data collection period. Individuals who developed melanoma and were diagnosed and treated were characterized further by whether they remained in remission, had a recurrence, were diagnosed with additional tumors or distant metastases, or died, as well as by an age-specific all-cause mortality risk.

Health outcomes in the model included QALYs, counts of melanomas and squamous-cell carcinoma, and melanoma-related deaths. Resources and costs included both those of government health providers (monitoring participants, cost of sunscreen, diagnosis, treating, and following suspicious skin lesions) and household members (time and out-of-pocket costs for applying sunscreen, attending clinic visits,

and a discounted lifetime cost following a diagnosis of melanoma. The cost of melanoma was taken from a previous study and inflated to 2010 prices.

According to the investigators, the data analysis showed that daily sunscreen use was significantly associated with prevention of invasive melanoma. Self-reported time spent outdoors, time in the shade, and wearing a hat were not significant predictors of melanoma occurrence between the daily and discretionary users of sunscreen.

The ICER was calculated based on a willingness-to-pay threshold of AU\$50,000 (approximately US\$52,000) per QALY gained.

A discounted incremental cost per QALY gained from daily use of sunscreen was AU\$42,600 for melanoma. If squamous-cell carcinoma was also included, the ICER per QALY was lower, at AU\$40,900. The model showed that the use of daily sunscreen would prevent 168 squamous-cell carcinomas, 33 melanomas, and 4 melanoma-related deaths at an additional cost of AU\$808,000 to

society in population with an average age of 49 years. Additional or fewer cases would be dependent upon the age when daily sunscreen is initiated.

The researchers found that daily sunscreen use was cost-effective for individuals aged between 38 and 64 years. The likelihood that daily sunscreen use is cost-effective for melanoma was 64%.

Promoting frequent sunscreen use is likely to be cost-effective for preventing melanomas and squamous-cell carcinomas. The effect on basal-cell carcinomas and the known protective effect of sunscreen use on actinic keratosis was not included; thus, the cost-effectiveness is most likely underestimated. This analysis supports that not only is sunscreen use effective and safe, it is also cost-effective. **EBO**

Source: Hirst NG, Gordon LG, Scuffham PA, et al. Lifetime cost-effectiveness of skin cancer prevention through promotion of daily sunscreen use. *Value in Health*. 2012;15:261-268.

### Payer Perspective

## Basing Coverage Decisions on Weak Comparators in Advanced Melanoma

James T. Kenney, RPh, MBA



Payers have become intensely interested in managing oncology drugs over the past few years, and health plans have increasingly deployed utilization management techniques in an attempt to control the drug spend in this growing market. Over 900 compounds are in some phase of clinical development for the treatment of cancer,<sup>1</sup> representing a significant future clinical and budgetary impact on pharmacy programs.

The prevalence of advanced melanoma is increasing among the general population; however, it still represents a small proportion of the overall health plan patient population.<sup>2</sup> With a 5-year survival of only 15.2%, there is significant room for improvement in treating metastatic melanoma.<sup>2,3</sup>

Traditional treatments for metastatic melanoma have not been found through clinical trial data to be particularly effective in improving overall survival (OS). One of the products more recently approved for the treatment of metastatic melanoma (in 2011), ipilimumab, has been found to improve OS in a pivotal clinical trial using an unapproved vaccine as a comparator. Health plans prefer an approved comparator to evaluate the potential benefits of a new compound. Even with this caveat, the lack of strong evidence to support older treatments increases the likelihood that ipilimumab will be granted coverage status, with limited but reasonable restrictions focused on its targeted mechanism of action.

This is not an unusual situation. Health plans typically cover pharmaceuticals for cancer with limited restrictions under the pharmacy or medical benefit, based on the lack of clinical data to support alternative treatments. The ability to manage cancer treatments is driven by the opportunity to trade off therapies with established guidelines or comparative clinical data. If the health plan's clinical team can offer specific and credible alternative drugs for a specific cancer, then the cost of the product and the total treatment costs will be considered as part of the coverage decision.

Most health plans do not use QALYs or ICERs to make formulary decisions. The formulary process primarily focuses on the core clinical parameters from the pivotal clinical trials, including OS, progression-free survival (PFS), and overall response rate (ORR). However, the cost-effectiveness analysis of ipilimumab by Barzey and colleagues<sup>4</sup> presents an interesting case for coverage based on the cost per QALY and ICER, using best supportive care as the comparator. The modeling focused on direct costs, including severe adverse events that can significantly affect costs, and incorporated the OS and PFS data. The results suggest the effectiveness of ipilimumab in patients compared with best supportive care to be 99%.

A cost per QALY in excess of \$100,000 will not resonate with health plans, owing to the relatively short time horizon for the clinical benefit of the product (just shy of 2 years).

As additional agents are approved by the FDA, payers will have better comparators for the evaluation of OS, PFS, or ORR in advanced melanoma and be ready for any opportunity to promote utilization management tools in support of guidelines and the most cost-effective care pathway.

Because virtually all cancer agents are approved for coverage by health plans, with varying tools to encourage appropriate use, the willingness-to-pay discussion by Barzey et al<sup>4</sup> does not typically occur at the health plan level. The finding of a durable benefit in 20%<sup>4</sup> of the patients will support the argument to provide access to the medication, and plans will not be overly restrictive, despite the lack of reasonable clinical comparators. The long-term survival benefit supports reasonable access for the product while plans monitor future drug approvals that may better target and treat metastatic melanoma.

Health plans will continue to evaluate new agents and strive to promote the most cost-effective options supported by solid clinical evidence. Although the analysis yields results in the range that is perceived to be acceptable to payers, most payers do not use these data in support of formulary decisions. At the end of the day, a new agent that demonstrates an OS benefit in metastatic melanoma will be covered by most plans.

*Mr Kenney is pharmacy operations manager at Harvard Pilgrim Health Care in Wellesley, MA.*

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# Crossroads in Breast Cancer: The Intersection of Clinical Uncertainty and Molecular Profiling

Kim Farina, PhD

At SABCS 2012, experts in the field provided an update on the use of molecular testing to guide treatment selection for in situ carcinoma of the breast, early-stage intermediate-risk estrogen-receptor-positive and triple-negative breast cancer, and metastatic disease.

**M**olecular oncology has brought a new understanding of carcinogenesis and has revolutionized the way we think about treating cancer.

Oncologists believe they are at a turning point in terms of how to use molecular assays now and in the not-too-distant future. "We are beginning to realize that we have only just scratched the surface," said Peter Ravdin, MD, PhD, UT Health Science Center San Antonio, who chaired an educational session titled *The Practical Use of Molecular Profiling* at the 2012 CTCR-AACR San Antonio Breast Cancer Symposium (SABCS). "It is pretty exciting, actually." The field is moving away from making decisions based on qualitative, descriptive prognostic information and moving toward precision medicine that is based on quantitative predictions.

Lawrence Solin, MD, Albert Einstein Medical Center, talked about molecular profiling of in situ carcinoma. Recent studies suggest that in situ disease is relatively advanced in its molecular progression to invasion, despite its distinct histologic appearance. National Comprehensive Cancer Network guidelines do not recommend molecular profiling for ductal carcinoma in situ (DCIS) or lobular carcinoma in situ, although estrogen receptor (ER) status is recognized as a tumor marker for DCIS.<sup>1</sup>

Whole breast irradiation (XRT) is known to reduce local recurrence among women who undergo lumpectomy for DCIS. Randomized trial data have demonstrated that radiation plus tamoxifen reduces risk for patients with estrogen receptor (ER)-positive tumors. In practice, it is difficult to distinguish low-risk patients using clinical

and pathological factors. "These are aggressive treatments for low-risk patients who rarely die of this disease," said Dr Solin.

Researchers who have developed a 12-gene signature assay for DCIS hope their system will address the problem of who to treat with adjuvant XRT. Initial results of their findings were presented at the 2011 SABCS and are under review for publication.<sup>2</sup> Investigators anticipate that this type of assay, once incorporated into widespread use, will support individualized treatment decision making and identification of molecular biology underlying DCIS.

Dr Solin participated in an analysis that compared the cost-effectiveness of basing decisions of whether to use adjuvant XRT on the 12-gene score versus routine clinical practice. Results of the analysis were presented as a poster at the 2012 SABCS.<sup>3</sup> The average cost of the 12-gene assay was lower than that of standard clinical assessment by approximately \$1000 per patient. Changing strategy from using the assay to clinical assessment was associated with an incremental cost-effectiveness ratio of approximately \$95,000 per quality-adjusted life-year. Estimates assumed that XRT benefits were independent of biology and that  $\geq 75\%$  of patients would not receive XRT.

For early-stage breast cancer, decisions regarding the use of adjuvant chemotherapy have considered hormone status of the tumor. With respect to tumor markers for breast cancer, the American Society of Clinical Oncology recommends ER and progesterone receptor (PgR) testing for decisions on endocrine therapy, and human epidermal growth factor (HER2) testing for deci-

sions regarding anti-HER2 and anthracycline therapy.<sup>4</sup> For prognosis, the 21-gene recurrence score (Oncotype DX breast cancer assay, Genomic Health, Inc), urokinase plasminogen activator, and plasminogen activator inhibitor for prognosis are recommended. The 21-gene recurrence score may also be used to help make treatment decisions; patients identified with a high-risk recurrence score are more likely to benefit from chemotherapy. This is not surprising, explained Antonio Wolff, MD, Johns Hopkins Kimmel Cancer Center, because nearly one-third of the non-reference genes in the assay are markers of proliferation, a trait that makes tumors particularly vulnerable to chemotherapy.

Gene expression array analyses have further refined tumor classifications. As additional molecular information is emerging, it is becoming clear that breast cancer should be viewed as a biologic continuum, not as discrete categories. "We know that [these categories] are not enough," said Dr Wolff. The validated predictive biomarkers have a strong negative predictive value; if the markers are not expressed, targeted therapy is not indicated. With a modest positive predictive value, however, they don't specifically ensure that patients who have receptor-positive tumor markers will benefit. "They also don't tell us in absolute terms whether to give it. For prognostic utility, you have to incorporate clinicopathologic measures of prognosis such as tumor size and node status for baseline assessment of risk."

At this point, clinicians and researchers are realizing that standard clinical measures and molecular assays do not provide the same information. "One assay, one method, is not necessarily better than the other," said Dr Wolff, emphasizing that clinical context matters. "The question is whether they can be complementary. What we need now are exercises where we are able to combine both molecular and clinical standard

information and try to improve on the prediction of what to do."

To answer some questions about how to use these assays, the field is awaiting the results of 2 completed prospective randomized trials: the Trial Assigning Individualized Options for Treatment (Rx) (TailoRX) and the Microarray for Node-Negative Disease may Avoid Chemotherapy (MINDACT).<sup>5</sup> TailoRX will attempt to answer the question of whether adding adjuvant chemotherapy to endocrine therapy will improve outcomes of patients with ER-positive, node-negative breast cancer and an intermediate-risk recurrence score (by the 21-gene assay). MINDACT will examine outcomes when chemotherapy is added to endocrine therapy in patients with discordant tumor risk assessments as determined by *Adjuvant! Online* and the 70-gene signature (MammaPrint, Agendia).

Tumor classification will improve with continued research. Building on established molecular information, the Cancer Genome Atlas recently reported the molecular portrait of over 800 breast tumor tissue samples, incorporating a host of biological factors, including phenotype, genotype, proteomics, epigenetics, copy number variation, and mRNA expression.<sup>6</sup> The analyses confirmed the existence of 4 major molecular subtypes of breast cancer: HER-2 enriched, luminal A, luminal B, and basal-like. "Much of the prognostic variability seems to be happening within these groups," said Dr Wolff. Yet, the usefulness of the data set is limited without a correlation to clinical outcomes. "As we move into the era of precision medicine, I think we need to begin to correlate this kind of information with clinical outcomes so that we can begin to make decisions," he said. Along with other studies, this study is also beginning to tease out different molecular subtypes underlying triple-negative breast cancer.<sup>6,7</sup>

Multiple studies have been examining how and to what extent available assays are being put into practice. One of the largest of these studies used the NCCN registry database to assess the adoption of gene expression profiling (GEP) and use of chemotherapy for women with hormone-receptor-positive breast cancer at 17 centers.<sup>8</sup> They found an absolute increase of



Lawrence Solin, MD



Antonio Wolff, MD

12% in GEP use ( $P < .01$ ) from 2006 to 2008 and an absolute decrease of about 5% in chemotherapy use ( $P < .01$ ) over the same time period ( $N = 7375$ ). Testing was associated with lower odds of chemotherapy use (odds ratio [OR], 0.70; 95% confidence interval [CI], 0.62-0.80), overall. However, Dr Wolff noted an interesting observation: physicians might have ordered the 21-gene assay to help confirm their underlying intent. Patients with node-positive and large node-negative cancers were less likely to receive chemotherapy (OR, 0.11; 95% CI, 0.07-0.17) while those with small, node-negative cancers were more likely to receive chemotherapy after GEP testing (OR, 11.1; 95% CI, 5.39-22.99). This suggested an underlying assumption by the clinician that one test might be more informative than the other. Patient factors also may have influenced GEP test ordering; the odds of being tested were lower for blacks versus whites (OR, 0.70; 95% CI, 0.54-0.92) and for those with high school education or lower versus those with a higher education (OR, 0.63; 95% CI, 0.52-0.76).

Despite a great deal of exciting investigational activity on molecular profiling of metastatic disease, relatively little has carried over to actual routine

**“Molecular analysis of tumors to find intriguing potential targets is readily available; the real bottleneck of progress is how to prove or disprove the clinical utility of these technologies.”**

—Lajos Pusztai, MD  
Yale Cancer Center

clinical use. “Sadly enough, there is no genomic test that is used routinely in the management of metastatic breast cancer today,” lamented Lajos Pusztai, MD, Yale Cancer Center. More often, for metastatic breast cancer, molecular markers are being used as patient selection criteria or to enrich a specific population in clinical trials.

In some select cases, repeating ER, PgR, or HER2 tests can be justified; for

example, when the diagnosis of a solitary nodule is in doubt, on technical grounds, in clinical trial, or when the clinical course of disease suggests different biology than the original receptor test result indicates. Considering test results in the clinical context is critically important. “For example, if a patient originally diagnosed with ER-negative breast cancer has recurrence 5 or more years after original diagnosis, this would be atypical,” explained Dr Pusztai. “In this setting, repeating a biopsy could be very important. If the patient turns out to be hormone receptor-positive on repeat testing, you could extend the life of that patient by years by offering hormone therapy.”

It is important to understand that a single repeat of the same test does not improve accuracy of the result. A 90% accurate test repeated twice on the same sample yields concordant results about 81% of the time ( $0.9 \times 0.9$ ) because 10% of the 90% of correct classifications from the first round will be misclassified in the second round and vice versa.

Because there is a cognizance bias to act on the most recent results, discordant results can be problematic and potentially dangerous, said Dr Pusztai. Yet, outside of a known technical error in the first test, there is no reason why the most recent test would be more accurate than the first. He recommends that if a patient has at least 1 positive result, at least 1 targeted agent should be tried.

Circulating tumor cells appear promising as a prognostic indicator for metastatic breast cancer, but are not of clinical utility in treatment selection. “One of the most important future challenges is to design experimental and informatics tools that could guide how to combine targeted agents to match the multiple abnormalities that individual cancers have that we can now readily measure,” said Dr Pusztai.

Clinical studies, as well as private and grant-funded entities, are now bringing high-throughput genomic analysis to cancer care with the goal of therapy tailored to a tumor’s molecular abnormalities.<sup>9-12</sup> In practice, however, clinicians are faced with the problem of what to do with the results.

In an interview after the session, Dr Pusztai talked about a hypothetical scenario with a patient who has meta-

static disease, has tried all available established therapies, has a molecular profile showing an epidermal growth factor receptor (EGFR) mutation, and is asking for an additional line of treatment with an EGFR inhibitor. “It would be great to know if that worked,” said Dr Pusztai. “It would be great to have a means to collect information on this—whether patients in those types of scenarios responded to a certain drug.” But, these therapies are expensive, most patients cannot afford them, and insurance companies are not likely to be willing to pay for these types of off-label treatment.

From a systems perspective, it is currently hard to prospectively collect outcomes data of this type of molecularly directed treatment approach in academic centers, explained Dr Pusztai. “At this point, off-label use of molecularly targeted drugs is too expensive without proper funding. Individual molecular abnormalities (eg, EGFR mutation in breast cancer) are

rare; access to many different off-label drugs would be needed in order to offer some therapy for most molecularly tested patients and learn from their experience,” he explained. Dr Pusztai would like to see insurance companies and the Centers for Medicare & Medicaid Services explore reimbursement for approved molecularly targeted drugs administered in the context of clinical studies that collect outcome information systematically. That type of information could provide grounds to build subsequent large definitive clinical trials to follow up on drugs that show activity in molecularly selected patient populations. “Molecular analysis of tumors to find intriguing potential targets is readily available; the real bottleneck of progress is how to prove or disprove the clinical utility of these technologies,” said Dr Pusztai. **EBO**

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Lajos Pusztai, MD

# Newly Discovered Biomarkers Predict Response in AML

Henri Stanton

Acute myeloid leukemia (AML) is the most common acute leukemia diagnosed in adults, and most patients with AML relapse after achieving complete remission with induction therapy. Most patients with AML die from relapsed disease. Therefore, biomarkers that accurately predict outcome in AML are needed so patients can be matched to the most appropriate therapies, according to presenters at the American Society of Hematology 54th Annual Meeting.

Extensive mutational testing can be used to refine prognostication in AML and inform therapeutic approaches, said Ross L. Levine, MD, Memorial Sloan-Kettering Cancer Center, New York, NY. Novel disease alleles in AML are mutations in *TET2*, *ASXL1*, *IDH1* and *IDH2*, *PHF6*, and *DNMT3A*. Integrated genetic analysis from 502 patients with AML enrolled in the Eastern Cooperative Oncology Group (ECOG) E1900 clinical trial revealed several genes with prognostic importance. Mutations in *IDH2* R140,

but not *IDH2* R172 or *IDH1*, were associated with improved survival. Mutations in *ASXL1* and *PHF6* were associated with worse overall survival.

Risk can be further refined in patients with intermediate-risk AML by more extensive mutational analysis, said Dr Levine. Three distinct risk groups can be identified in *FLT3*-ITD-negative intermediate-risk AML based on mutational status; *TET2*, *ASXL1*, *PHF6*, and partial tandem duplications in *MLL* are poor-risk mutations associated with worse survival in the group of intermediate-risk patients with wild-type internal tandem duplications in *FLT3*.

In the ECOG E1900 trial, a post hoc analysis of mutational status found that high-dose daunorubicin improved outcomes markedly for patients with *DNMT3A* mutations. Patients with *NPM1* or *DNMT3A* mutations, or *MLL* translocations, had a 3-year overall survival rate of 44% with high-dose daunorubicin induction chemotherapy compared with

25% rate when treated with standard-dose daunorubicin.

Minimal residual disease (MRD) after treatment in AML predicts failure to maintain a morphologic complete response and negatively affects survival. Elisabeth Paietta, PhD, professor, department of medicine (oncology), Albert Einstein College of Medicine of Yeshiva University, Bronx, NY, reviewed approaches to monitoring MRD, noting that the best method is still a matter of debate and that MRD assessment assays need to be standardized. They are either immunophenotypic, done by multiparameter flow cytometry, or done by polymerase chain reaction to detect recurrent gene mutations or leukemia fusion transcripts. Very sensitive assays, perhaps next generation sequencing, are needed to find minor clones present at diagnosis that may lead to relapse. Even with detection of MRD, therapeutic options at present are limited, she said. Intensive therapeutic approaches have not worked in MRD-positive pa-

tients, said Dr Paietta.

Relapsed AML remains a clinical challenge, said Jeffrey Szer, MBBS, professor/director, department of clinical haematology and BMT service, The Royal Melbourne Hospital, Parkville, Australia. Novel approaches to the treatment of relapse include clofarabine, a novel purine analogue, with or without cytarabine; tosedotat, an orally available aminopeptidase inhibitor that has shown significant clinical activity in a phase I/II study; and *FLT3* inhibitors, which may have a role as a bridge to transplantation. Inhibitors of the mammalian target of rapamycin (mTOR), such as everolimus and sirolimus, have potential utility given the role of the mTOR pathway in cytarabine activity. Hypomethylating agents are being studied as maintenance therapy after allo-stem cell transplant (SCT). Allo-SCT has the potential to cure relapsed or refractory disease, but only after patients have achieved a second complete remission or MRD. **EBO**

# Evidence-Based Approaches to Cytopenias Discussed

Henri Stanton

Diagnostic approaches to cytopenias require an understanding of their etiology, said presenters during the American Society of Hematology 54th Annual Meeting.

Neutropenia is often a secondary finding “to a far more significant underlying hematologic disorder, placing the patient at risk for infectious complications,” said Laurence A. Boxer, MD, a pediatric hematologist-oncologist at the University of Michigan Health System, Ann Arbor.

In the case of severe congenital neutropenia (SCN), which is characterized by recurrent severe infections during the first months of life, bone marrow examination characteristically shows a myeloid “maturation arrest” at the promyelocyte-myelocyte stage of development. Mutations in the *ELANE* gene have been observed in 40% to 60% of patients with congenital neutropenia, and neutropenia caused by the *ELANE* mutation is associated with the most severe infectious complications, Dr Boxer said.

An autosomal-recessive subtype of SCN is Kostmann disease, in which mutations of the *HAX1* gene are observed. Patients with both isoform A and isoform B *HAX1*-spliced variants can suffer

from neurologic impairment that ranges from developmental delay to severe epilepsy.

Uncovering the cause of chronic anemia relies on a complete blood count (CBC), said Mark J. Koury, MD, professor of medicine, division of hematology/oncology, Vanderbilt University, Nashville. The 4 patterns encountered frequently in CBCs associated with chronic anemia are anemia with abnormal platelets and/or leukocyte counts, anemia with increased reticulocyte counts, a lifelong persistence of an abnormal CBC, and anemia with inappropriately low reticulocytes.

Diseases affecting early-stage hematopoietic progenitors, such as liver disease, will likely affect platelets and leukocytes. Underlying causes can include chronic alcohol intake and antiviral treatments for hepatitis C. The absence of an enlarged spleen usually indicates a primary bone marrow disease, including myelodysplasia or malignant invasion of the bone marrow, such as with multiple myeloma.

An increased number of reticulocytes with chronic anemia indicates low-grade hemolysis or blood loss (possibly from upper gastrointestinal lesions or menorrhagia). Erythrocyte fragmentation on the blood smear is often as-

sociated with malignant tumors, large hemangiomas, prosthetic heart valve defects, or direct external trauma, said Dr Koury. Spherocytes suggest hereditary spherocytosis or immune hemolysis, the latter of which can be diagnosed by surface antibodies and/or complement components on erythrocytes in the direct antiglobulin test.

Bone marrow events responsible for low reticulocyte production include apoptosis of erythroid progenitor and precursor cells by intrinsic and extrinsic factors, development of macrocytosis when erythroblast DNA replication is impaired, and development of microcytosis due to heme-regulated eIF2- $\alpha$  kinase inhibition of protein synthesis in iron-deficient or thalassemic erythroblasts.

Correct identification of the cause of thrombocytopenia is crucial for proper management, said Roberto Stasi, MD, PhD, department of haematology, St. George's Hospital, London, UK. Thrombocytopenia may be the initial manifestation of infections (ie, HIV and hepatitis C virus). Examination of the peripheral blood smear remains the most important investigation to guide diagnostic approaches. Liver and renal function tests, a clotting screen with D-dimers,

and measurement of lactate dehydrogenase are part of the basic laboratory evaluation.

A bone marrow aspirate and biopsy may be performed if the etiology of the thrombocytopenia is unclear, said Dr Stasi.

Primary immune thrombocytopenia (ITP) remains a diagnosis of exclusion, he said, with no consensus on the set of investigations. The role of the bone marrow biopsy and aspirate in ITP are controversial.

Thrombocytopenia in the hospitalized patient has many possible etiologies; special consideration should be given to drug-induced thrombocytopenia considering its frequency in this setting, said Dr Stasi. Heparin-induced thrombocytopenia is often a clinical emergency and typically develops after 5 to 10 days of exposure to heparin. **EBO**

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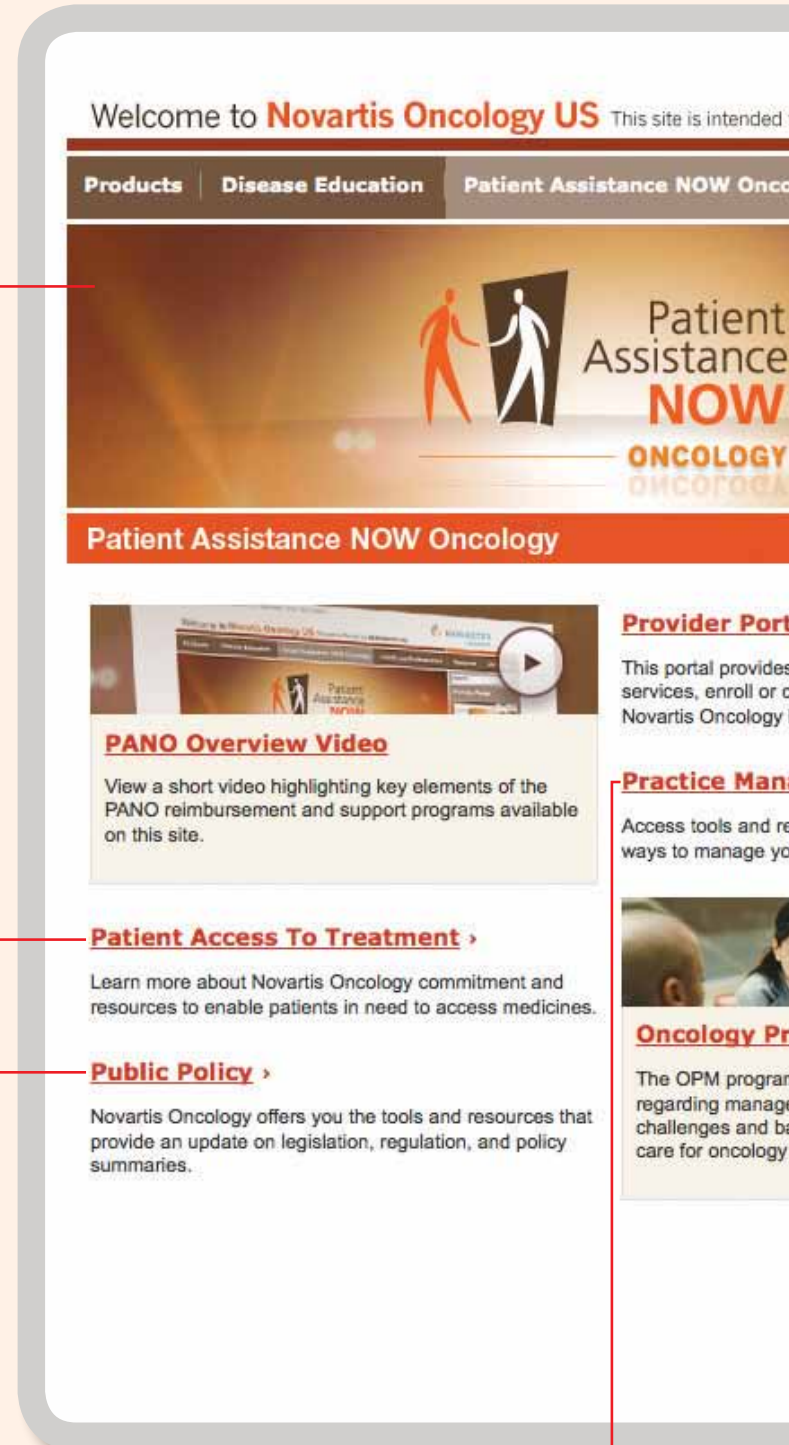


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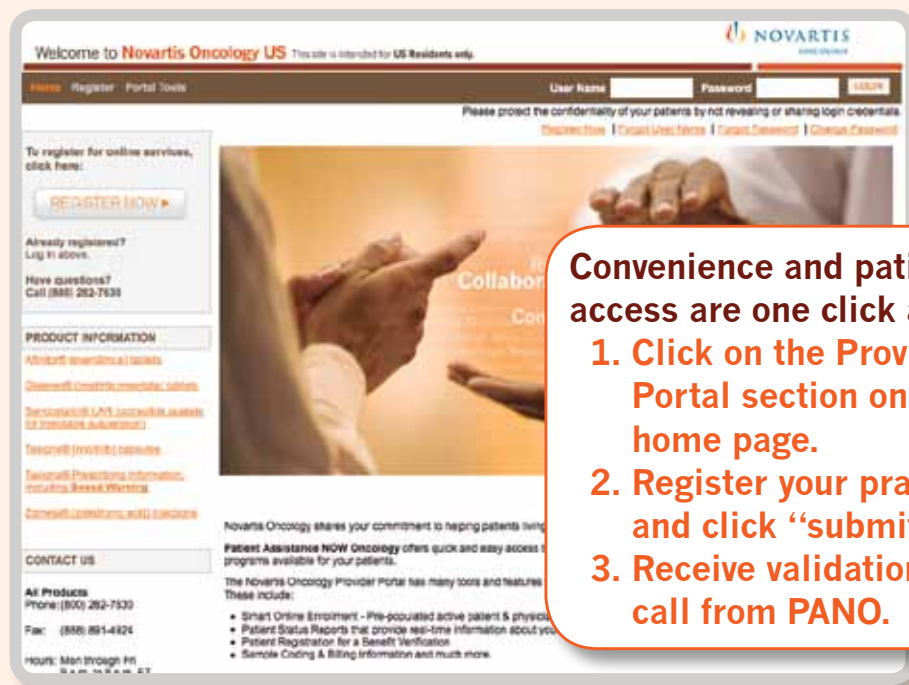
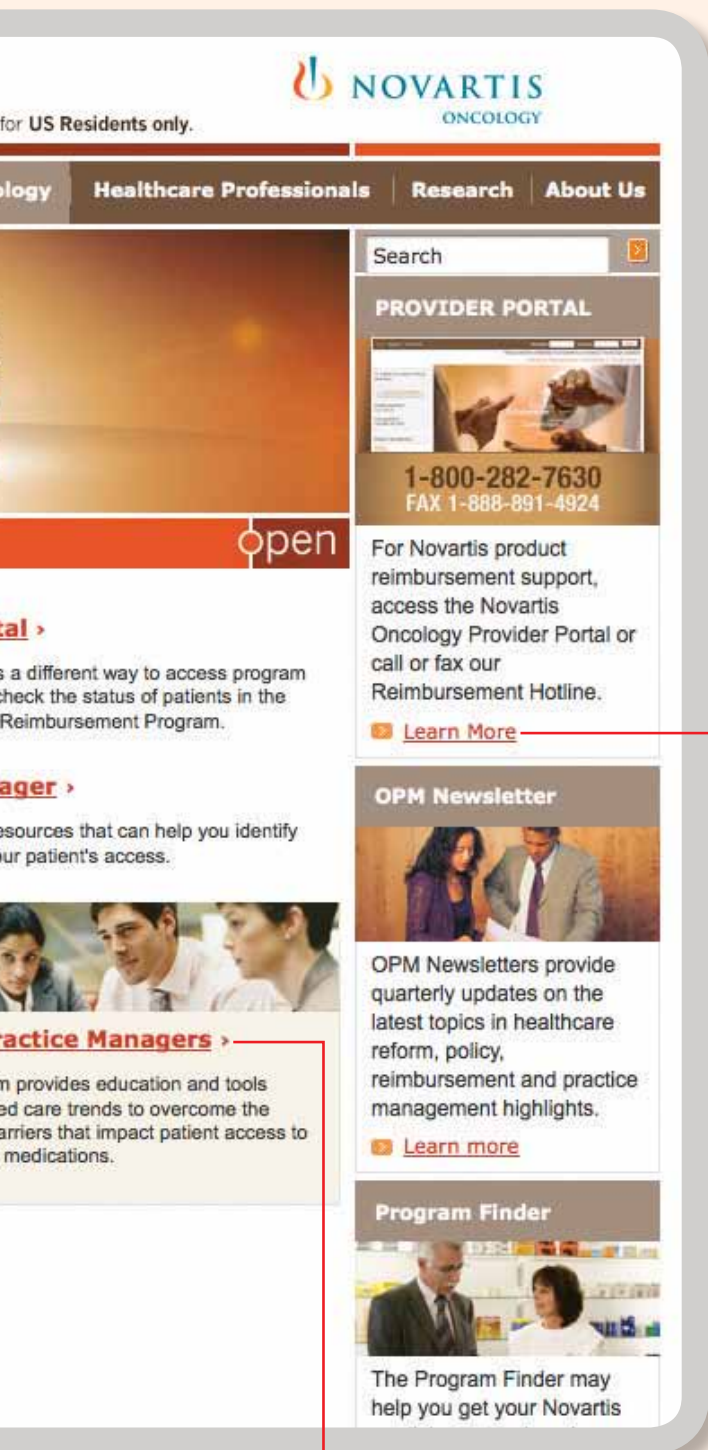
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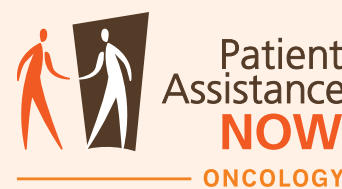
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Helping to make access to therapies easier

# Managed Care Restrictions: Barriers to Product Use in Cancer Care

Lisa A. Fox



set of guidelines for how they manage patients. The problem is you're dealing with expensive drugs, and we have a fiduciary responsibility to make sure what the employer is paying for is appropriate, and to keep the physicians honest....When you have a third party paying for it, they have a right to a say on how it's being spent."

As demonstrated in HRA's study, *Changing Paradigms in Managed Care—Oncology Management*, surveyed oncologists and oncology nurse navigators clearly are not pleased with the trends toward increased PA use.

"Who's going to be calling for all these approval[s]?...I've got somebody that's got metastatic cancer. They need to be treated now—not a month from now, not 3 months from now," stated an oncologist participating in HRA's study. "We spend a lot of time in trying to do the best...for our patients [to get treatments] approved and it basically delays care."

### More Stringent Guidelines

In fact, the use of more stringent prior authorization guidelines will lead about half of the 100 medical oncologists participating in the research to reconsider their first-choice oncologic

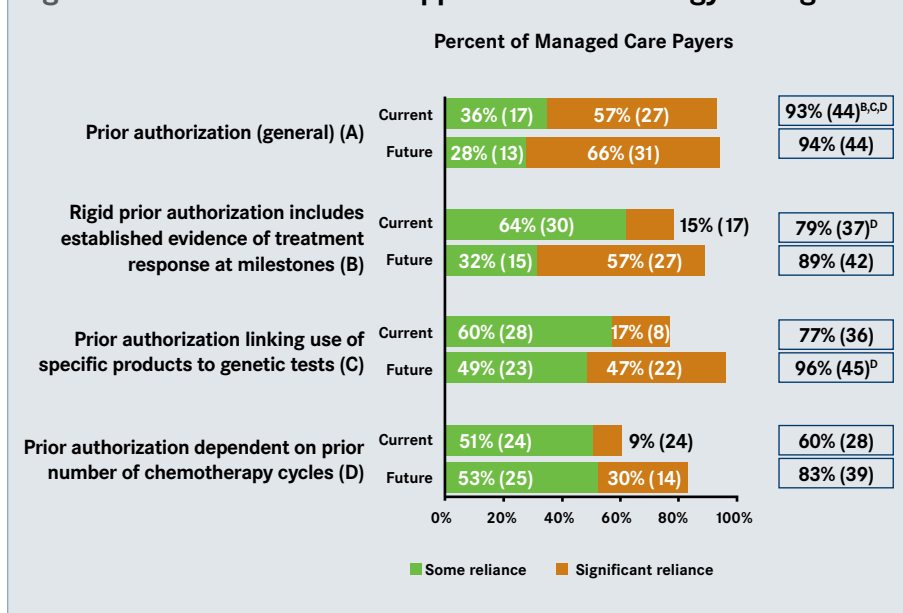
Across specialties, prior authorization (PA) is the bane of physicians and their office staff. Once employed as a utilization management tactic primarily for more benign therapeutic classes, it is now a ubiquitous force in oncology management—one that is expected to become even more targeted beyond US Food and Drug Administration (FDA) indication alone.

### Prior Authorization

Recent research conducted by HRA (Healthcare Research & Analytics, a market research consultancy based in Parsippany, New Jersey) reveals that 93% of the 47 major health plans included in its recent study routinely employ PA to manage utilization of oncology agents. Over three-fourths of these payers, which cover over 100 million lives in total, place at least some reliance on rigid PA that links approval with product efficacy at specific milestones, or rely on PA to ensure that the appropriate biomarker tests are conducted prior to approval of specific agents. In the future, the use of more stringent PA criteria is expected to increase significantly—with nearly 90% of the plans intending to link PA to specific treatment milestones and even more planning to link PA with genetic testing (Figure 1).

"Any specialty other than oncology, this is the way you'd do it—fairly rigid according to what the evidence has shown," states one key opinion leader participating in the research who is employed by a major US payer organization. "Oncologists want a separate

Figure 1. Reliance on Current Approaches to Oncology Management



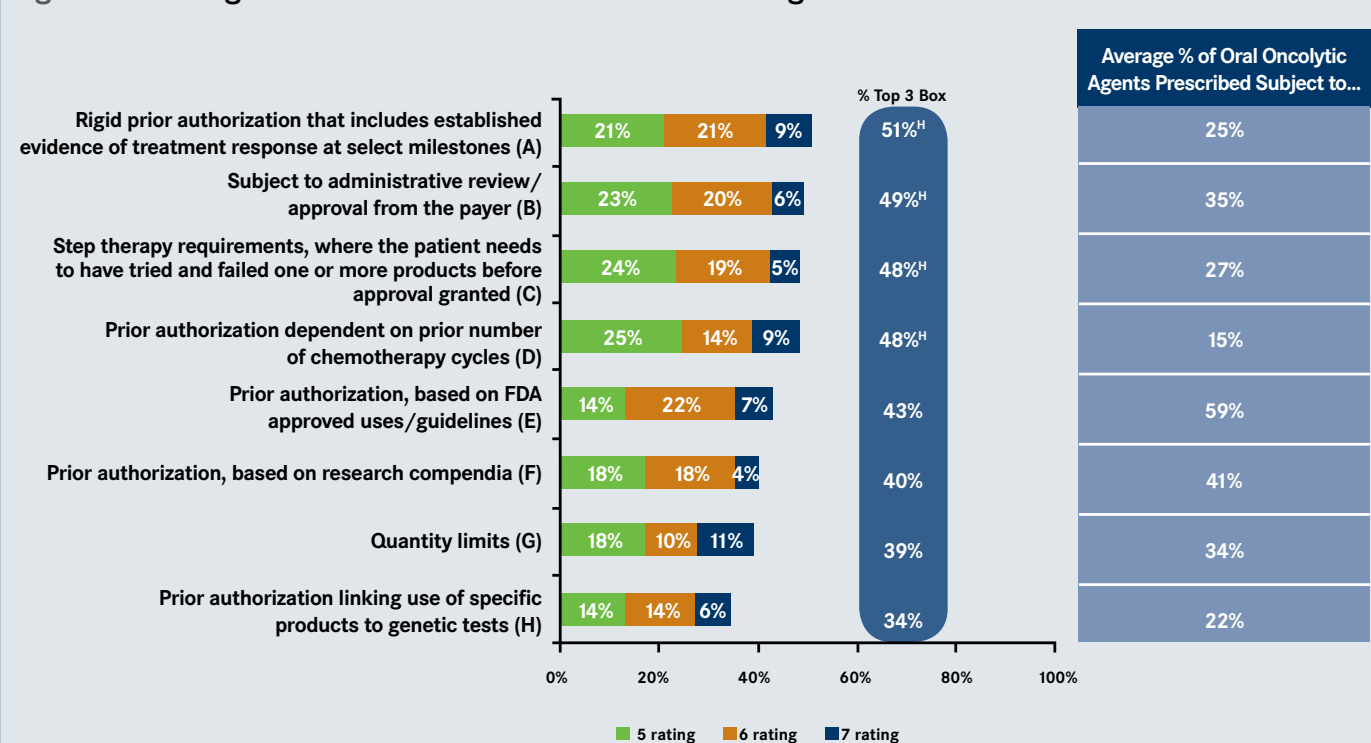
Items ranked based on the net reliance; statistical testing based on net reliance.

agent due to the hassle factor that PA presents (Figure 2). PA based on product efficacy at select milestones or on the number of treatment cycles, as well as step therapy requirements enforced via PA, serve as the primary deterrents, whereas oncologists are less fazed by the idea of payers requiring specific

biomarker/genetic tests before approving the associated agents. Fortunately, for the oncologists and the patients they treat, widespread use of PA beyond FDA indication alone is not occurring—yet.

Although managed care is including general PA as a requirement for over

Figure 2. Oncologist Likelihood to Reconsider First-Choice Agent Due to Restrictions



FDA indicates US Food and Drug Administration.

**Table. Managed Care Restrictions for Oral Oncolytics**

	Current % of Agents Subject to Restriction (A)	% of Agents Will Be Subject to Restriction Next 2-3 Years (B)
Prior authorization, based on FDA-approved uses/guidelines	67%	73%
Quantity limits	59%	62%
Prior authorization, based on research compendia	53%	61%
Use subject to administrative review	32%	33%
Prior authorization that includes frequent treatment response monitoring	20%	35%
Approved use linked to results of diagnostic tests	15%	34% <sup>A</sup>
Step therapy requirements	14%	31% <sup>A</sup>
Prior authorization, including a baseline of number of prior chemotherapy cycles	13%	27% <sup>A</sup>
Other restriction	3%	3%

Items ranked based on the current percentage.  
FDA indicates US Food and Drug Administration.

two-thirds of oncology agents, on average, more stringent PA is just emerging. PA based on patient response to specific treatments, on biomarker/genetic testing, and as a means to enforce step therapy is currently in place for one-fifth or less of agents, though significant increases in prevalence are expected over the next few years (Table).

The growing presence of step therapy poses a disadvantage for new oncology agents—logistically as well as conceptually—as oncologists maintain strong perceptions that new oncolytic agents are very likely to be subject to PA. Agreement with this concept is noted among over 80% of oncologists in the research. Further, nearly 2 out of 3 oncologist participants point to PA as a deterrent to prescribing new agents (Figure 3).

“[There will be] a lot more prior authorization, a lot more attempt to engage oncologists around pathway adherence, and end-of-life discussions earlier in the course of therapy,” said a

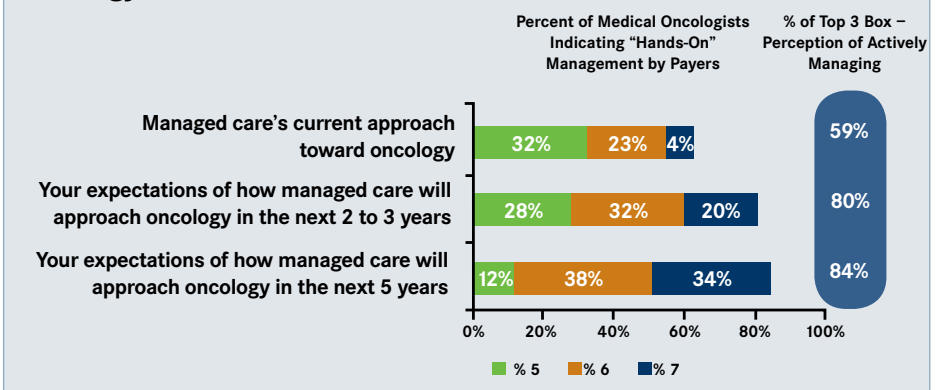
key opinion leader participating in the research, “because these are felt to be the biggest variables that contribute the most to cost.”

**Heavily Managed**

Increased PA, the development of clinical pathways programs, and high copays/co-insurance levels are leading oncologists toward perceptions of oncology as now being a “heavily managed” category. While over half of oncologists currently perceive payers as providing hands-on management of oncology, 8 in 10 oncologists predict that active management will be the norm 2 or 3 years from now (Figure 4A). Further, those oncologists who have more negative perceptions of payers and their involvement in oncology are more inclined to suggest that payers will be more stringent in both the short and long term (Figure 4B).

“There is a new intensity of scrutiny from the payer side, a significant increase

**Figure 4A. Level of “Active” Management Employed by MCOs for Oncology**



in protocols and other management constraints on oncology,” said one of the key opinion leaders participating in the research. “Across all lines of business, saying ‘We’re not going to pay for everything, and if we are, we need to have some understanding of medical necessity, and the rationale around morbidity, mortality, and patient improvement.’”

By 2015, oncolytic agents are predicted to be the second- or third-greatest driver of total drug spend, an increase

Balancing the need for fiscal soundness with public policy considerations as well as—most importantly—the need to provide patients with the most effective treatments is a fine line for payers, one that continues to fray with each new expensive oncology treatment that comes to market. **EBO**

**Author Affiliation:** From Healthcare Research & Analytics, Parsippany, NJ.

**Funding Source:** None.

**Figure 4B. Percent of Oncologists – Strongest Agreement<sup>a</sup> Ratings That Managed Care Will Become More “Hands-On” in Management**

Oncologists with a...	More Negative Experience with Payers (A)	More Positive Experience with Payers (B)
In the next 2 to 3 years	75%	45%
In the next 5 years	91%	64%
	(n = 32)	(n = 42)

<sup>a</sup>Percent Top 2 Box.  
MCO indicates managed care organization.

from seventh place in 2011.<sup>1</sup> By 2020, total cancer costs are projected to reach \$158 billion.<sup>2</sup> To ensure their own fiscal survival, payers may be left with little choice but to increase controls in oncology, despite the potential backlash.

So the question remains—which direction will payers take in exerting greater control over the oncology category? Will novel approaches such as clinical pathways programs provide enough specific direction and incentive to control spend, or will payers need to resort to the more traditional mainstay of prior authorization to manage utilization? If prior authorization in oncology continues to evolve, just how far will payers be willing to go in the stringency of their requirements, without risking major repercussions among oncologists? And, will oncologist and payer affiliations in integrated delivery networks help enforce these approaches?

As one payer respondent participating in the research states, “We have a number of prior auth requirements on most of these agents, but are limited in our effectiveness by the strong public pressure and some special legal protections they enjoy.”

**Author Disclosure:** Ms Fox reports employment with HRA—Healthcare Research & Analytics, the company that produced this research. HRA is owned by MJH & Associates, which also owns *The American Journal of Managed Care*.

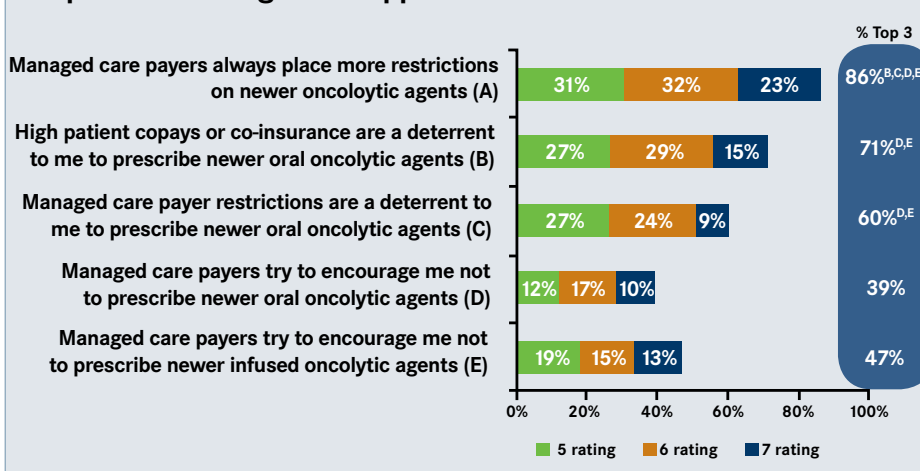
**Authorship Information:** Concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

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**Figure 3. Payer Management of Newer Oncolytics/Oncologist Response to Management Approaches**



# Partial Fill Strategies for Oral Oncolytics to Reduce Waste and Drive Persistency

Atheer A. Kaddis, PharmD



The number of drugs to treat cancer in the drug development pipeline, reportedly exceeding 900 as of 2012,<sup>1</sup> is both exciting and frightening to payers. Nearly half of the cancer medications currently in development are oral oncolytics, and with costs for these agents commonly exceeding \$50,000 to \$100,000 per patient per year, this could result in significant budgetary impacts for payers. There is no question that innovation can result in improved quality of care and reduction in morbidity and mortality rates

**An analysis of patients diagnosed with early-stage breast cancer showed that less than 50% of patients prescribed adjuvant hormonal therapy actually continued therapy for the full duration of the optimal schedule for treatment.**

for various cancers; however, payers struggle with ensuring that the right patient receives the right medication at the right time.

In the case of expensive self-administered medications, this also means ensuring that patients prescribed the right medication take the medication as prescribed and are adherent to the therapeutic regimen. This is easier said than done. An analysis of patients diagnosed with early-stage breast cancer showed that less than 50% of patients prescribed adjuvant hormonal therapy actually continued therapy for the full duration of the optimal schedule for treatment.<sup>2</sup> The same analysis showed that younger patients were even more nonadherent to therapy than older patients. Reasons for nonadherence included lack of patient counseling by their physician, toxicity from the therapeutic regimen, and out-of-pocket costs associated with the prescribed therapy.

In addition to lack of adherence (failure to take the medication as prescribed), common challenges also include failure in filling the initial prescription (noninitiation) and failure to continue the prescribed duration of therapy (early discontinuation).<sup>3</sup> Many strategies have been used to improve rates of adherence to self-administered therapies, including oral therapies, in the past. This article will shed light on a strategy requiring more frequent counseling of patients by patient care coordinators trained in oncology and the partnership they form with the patients to ensure improved adherence to potentially life-saving therapies.

#### Cost Trend Mitigation Strategies for Oral Oncolytics

While traditional drug cost trends are forecasted to be in the range of 0% to 5% per year over the next 2 years, specialty drug cost trends are expected to be in the range of 20% to 25% per year during the same time period.<sup>4</sup> In response to historical and forecasted drug cost trends for specialty drugs, payers have implemented various strategies to help mitigate these cost trends.

Strategies that have been and continue to be implemented include renegotiating contracts with providers to obtain more aggressive discounts, benefit cost strategies aimed at shift-

**Table 1. Diplomat Experience (June 1, 2010, to June 30, 2011)**

55.71% of patients stayed on therapy after initial partial fill
42.86% of patients discontinued therapy after first 2 partial fills
24.29% of patients discontinued therapy after 1 partial fill
1.43% of patients switched therapy after initial partial fill

ing more costs to patients through increased cost sharing, formulary management strategies aimed at a low net cost goal through preferencing of lower cost agents and/or obtaining larger rebate concessions from pharmaceutical manufacturers, utilization management strategies including step therapy and/or prior authorization to ensure medications are being prescribed in accordance to best practices and consensus guidelines, channel management strategies to ensure medications are dispensed or administered in the lowest cost site of care, and drug therapy management strategies to ensure patients are taking the most appropriate therapies and remaining adherent to prescribed therapies.

Innovation in all of these areas has been experienced over the past few years. One of the most recent innovations within drug therapy management, partial fill strategies for oral oncolytics, has led to some excitement within the payer and specialty pharmacy communities due to its impact on drug cost trends as well as improved, and more frequent, direct interaction between providers and the patients they are treating.

#### Partial Fill Strategies for Oral Oncolytics

The first published article on partial fill strategies for oral oncolytics focused on 3 oral oncolytics, including sorafenib (Nexavar), sunitinib (Sutent), and erlotinib (Tarceva).<sup>5</sup> In this program, monthly therapies for the 3 medications were split into 14-day and 16-day batches (partial fill) and out-of-

pocket cost share was also adjusted for the partial fill. In addition to the partial fill of the prescription, patients received education on the treatment regimen, the importance of adherence to therapy, and earlier identification of adverse events from the medications, and regular communication with the patients and their providers on measures to take to reduce dosages or discontinue therapy was provided.

The intervention group consisted of 1069 patients who were prescribed 1 of the 3 study medications during the time period of June 2008 through February 2010. The control group consisted of 351 patients who were prescribed 1 of the 3 study medications during the time period of January 2007 to May 2008 (before the inception of the partial fill program).

The authors demonstrated that 261 patients discontinued therapy in the first month of the program, and 7.7% could have saved at least one-half of the prescribed month of therapy. Overall, 33.8% of patients could have been prevented from wasting the prescribed oral chemotherapy medications through implementation of a partial fill program. Average savings per patient was \$934.20. The study also demonstrated that hospitalizations were reduced by 2.9%, resulting in average savings of \$439.87, in patients that received interventions within the partial fill program.

The results of this study have led to a rapid expansion of partial fill strategies being adopted by payers and an expansion in the number of oral oncolytics included in the partial fill programs.

**Table 2. Diplomat Experience (March 1, 2011, to March 1, 2012)**

45.71% of patients stayed on therapy after initial partial fill
52.00% of patients discontinued therapy after first 2 partial fills
15.43% of patients discontinued therapy after 1 partial fill
2.29% of patients switched therapy after initial partial fill

**Table 3. Oral Oncolytics Included in the Current Version of the Partial Fill Program**

Brand Name	Generic Name
Afinitor	Everolimus
Erivedge	Vismodegib
Gleevec	Imatinib
Inlyta	Axitinib
Jakafi	Ruxolitinib
Nexavar	Sorafenib
Sprycel	Dasatinib
Sutent	Sunitinib
Tarceva	Erlotinib
Targretin	Bexarotene
Tasigna	Nilotinib
Votrient	Pazopanib
Zelboraf	Vemurafenib
Zolinza	Vorinostat
Zytiga	Abiraterone

**Expansion of Partial Fill Strategies for Oral Oncolytics**

In early 2010, Diplomat Specialty Pharmacy implemented a partial fill program for payer clients focusing on enhanced outreach, education, and intervention for patients that were prescribed sorafenib (Nexavar), sunitinib (Sutent), or erlotinib (Tarceva). Patient outreach was provided telephonically twice per month by patient care coordinators, nurses, and pharmacists with specific training in oncology. Each outreach phone call was provided 5 to 7 days before the next partial fill was dispensed. Dispensing was provided in 14-day and 16-day batches.

Patient outreach included initial enrollment of the patient into an oncology patient care program, education of the patient on their diagnosis and prescribed therapy which included verbal communication as well as written education materials, assessment of adverse events reported by patients and what to do to mitigate adverse events, copay assistance support provided through non-profit charitable organizations, home delivery of prescribed medications and supportive therapies, and outreach to prescribing physicians to discuss alternative options for patients that could not tolerate the prescribed therapy.

Results of interventions were tracked for 12 months after the program was implemented (Table 1). Nearly 43% of patients discontinued therapy after the first month of the prescribed therapy with nearly 25% discontinuing therapy after 1 partial fill. The primary reason

for discontinuation was adverse events reported by patients.

Based on the results of the initial partial fill program rollout, the list of target medications for the program was expanded in early 2011 to include sorafenib (Nexavar), sunitinib (Sutent), erlotinib (Tarceva), everolimus (Afinitor), imatinib (Gleevec), dasatinib (Sprycel), bexarotene (Targretin), and pazopanib (Votrient). The same types of interventions were provided to patients in this phase of the program.

Results of interventions were tracked for 12 months after the program was implemented (Table 2). Fifty-two percent of patients discontinued therapy after the first month of the prescribed therapy, with more than 15% discontinuing therapy after 1 partial fill. The primary reason for discontinuation in this phase was adverse events reported by patients.

The current version of the partial fill oral oncolytic program includes 15 oral oncolytics (Table 3). The program was expanded to include all 15 oral oncolytics in early 2012. Specific oral oncolytics were targeted for the program due to high discontinuation rate due to poor response, adverse effects, and high rates of noncompliance.

Results of interventions were tracked for 9 months after the program was implemented (Table 4). 41% of patients discontinued therapy after the first month of the prescribed therapy with approximately 20% discontinuing therapy after 1 partial fill. Again, the primary reason for discontinuation in this phase was adverse events reported by patients.

**Table 4. Diplomat Experience (January 1, 2012, to September 30, 2012)**

59% of patients stayed on therapy after initial partial fill
41% of patients discontinued therapy after first 2 partial fills
20% of patients discontinued therapy after 1 partial fill
2% of patients switched therapy after initial partial fill

In addition to tracking discontinuation rates of therapy, potential drug cost savings has also been tracked (Table 5). For a payer that has approximately \$1M in annual spend for the targeted medications, the potential annual savings due to this program would be expected to exceed \$186,000 or 19% of total spend based on the average monthly cost of the prescription and the experienced discontinuation rates.

**Conclusion**

It is important to note that the purpose of partial fill oral oncolytic programs is not to reduce access to potentially life-saving therapies. The goal is to allow more frequent direct intervention and tracking of patients and their therapies by personnel specifically trained in oncology. The patient care coordinators, pharmacists, and nurses working within specialty pharmacies that reach out to patients regularly partner with patients and their physicians to promote high-quality care and improved adherence to therapy. While significant drug cost savings can be achieved with partial fill oral oncolytic programs, the focus must remain on the patient and ensuring that they are getting the best care possible.

In conducting these programs, there are 2 observations that require more study and understanding. One observation is related to the higher-than-expected rate of adverse events with the therapies. The incidence reported by patients was higher than that reported in clinical trials with these therapies and this should be investigated more thoroughly. The other observation was the incidence of mortality in patients within each phase of the program, which reached over 20% of patients that discontinued therapy after the first month of treatment. This also

needs further investigation to ensure that the specific medications are not being used in lieu of end-of-life care for patients. The answers to these questions will further our understanding of these important therapies and how they can impact the lives of patients diagnosed with cancer. **EBO**

**Author Affiliation:** From Diplomat Specialty Pharmacy, Flint, MI.

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**Authorship Information:** Concept and design; acquisition of data; analysis and interpretation of data; and drafting of the manuscript.

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**Table 5. Potential Plan Savings**

Plan spend	\$1M annually
Average cost/Rx	\$7048.04
Total Rx	142
Partial fill Rx	58
Annual savings	\$186,950 (19% of total spend)

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- ♥ **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.
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♥ **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.

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♥ **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.

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K08Z12176

**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 adrenocorticotrophic 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<sub>max</sub> and AUC<sub>0-∞</sub> (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)		Placebo with Prednisone (N=394)	
	All Grades <sup>1</sup> %	Grade 3-4 %	All Grades %	Grade 3-4 %
<b>Musculoskeletal and connective tissue disorders</b>				
Joint swelling/discomfort <sup>2</sup>	29.5	4.2	23.4	4.1
Muscle discomfort <sup>3</sup>	26.2	3.0	23.1	2.3
<b>General disorders</b>				
Edema <sup>4</sup>	26.7	1.9	18.3	0.8
<b>Vascular disorders</b>				
Hot flush	19.0	0.3	16.8	0.3
Hypertension	8.5	1.3	6.9	0.3
<b>Gastrointestinal disorders</b>				
Diarrhea	17.6	0.6	13.5	1.3
Dyspepsia	6.1	0	3.3	0
<b>Infections and infestations</b>				
Urinary tract infection	11.5	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
<b>Respiratory, thoracic and mediastinal disorders</b>				
Cough	10.6	0	7.6	0
<b>Renal and urinary disorders</b>				
Urinary frequency	7.2	0.3	5.1	0.3
Nocturia	6.2	0	4.1	0
<b>Injury, poisoning and procedural complications</b>				
Fractures <sup>5</sup>	5.9	1.4	2.3	0
<b>Cardiac disorders</b>				
Arrhythmia <sup>6</sup>	7.2	1.1	4.6	1.0
Chest pain or chest discomfort <sup>7</sup>	3.8	0.5	2.8	0
Cardiac failure <sup>8</sup>	2.3	1.9	1.0	0.3

<sup>1</sup>Adverse events graded according to CTCAE version 3.0

<sup>2</sup>Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

<sup>3</sup>Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness

<sup>4</sup>Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema

<sup>5</sup>Includes all fractures with the exception of pathological fracture

<sup>6</sup>Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia

<sup>7</sup>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).

<sup>8</sup>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)		Placebo (N=394)	
	All Grades (%)	Grade 3-4 (%)	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)		Placebo with Prednisone (N=540)	
	All Grades <sup>1</sup> %	Grade 3-4 %	All Grades %	Grade 3-4 %
<b>General disorders</b>				
Fatigue	39.1	2.2	34.3	1.7
Edema <sup>2</sup>	25.1	0.4	20.7	1.1
Pyrexia	8.7	0.6	5.9	0.2
<b>Musculoskeletal and connective tissue disorders</b>				
Joint swelling/ discomfort <sup>3</sup>	30.3	2.0	25.2	2.0
Groin pain	6.6	0.4	4.1	0.7
<b>Gastrointestinal disorders</b>				
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
<b>Vascular disorders</b>				
Hot flush	22.3	0.2	18.1	0.0
Hypertension	21.6	3.9	13.1	3.0
<b>Respiratory, thoracic and mediastinal disorders</b>				
Cough	17.3	0.0	13.5	0.2
Dyspnea	11.8	2.4	9.6	0.9
<b>Psychiatric disorders</b>				
Insomnia	13.5	0.2	11.3	0.0
<b>Injury, poisoning and procedural complications</b>				
Contusion	13.3	0.0	9.1	0.0
Falls	5.9	0.0	3.3	0.0
<b>Infections and infestations</b>				
Upper respiratory tract infection	12.7	0.0	8.0	0.0
Nasopharyngitis	10.7	0.0	8.1	0.0
<b>Renal and urinary disorders</b>				
Hematuria	10.3	1.3	5.6	0.6
<b>Skin and subcutaneous tissue disorders</b>				
Rash	8.1	0.0	3.7	0.0

<sup>1</sup>Adverse events graded according to CTCAE version 3.0

<sup>2</sup>Includes terms Edema peripheral, Pitting edema, and Generalized edema

<sup>3</sup>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 <sup>1</sup>	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

<sup>1</sup>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  $\geq 10$  mg/kg/day, decreased fetal ano-genital distance at  $\geq 30$  mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses  $\geq 10$  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.

**Storage and Handling:** Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F) [see *USP controlled room temperature*].

Based on its mechanism of action, ZYTIGA may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves [see *Use in Specific Populations*].

#### 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.

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# From Bench to Bedside: Promising Colon Cancer Clinical Trials

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Colorectal cancer (CRC) was the third-most common cause of cancer-related deaths in the United States in 2012, accounting for around 51,690 deaths. Approximately 143,460 people are diagnosed with CRC annually, making up 9% of all cancer diagnoses.<sup>1</sup> Specifically, colon cancer makes up 72% of the incidence of CRC, with rectal cancers accounting for the remaining 28%. CRC is more common in males and in the African American population compared with other ethnicities. Within the last 35 years, the mortality rates have been decreasing. The 5-year overall survival (OS) of CRC, a non-curable malignancy, is around 64.3%, with stage I disease being 89.9% and stage IV disease being 11.9%.<sup>2</sup>

The treatment of colon cancer depends upon the stage. For those who have operable disease, surgical resection is preferred. Patients with high-risk stage II or stage III disease should then receive adjuvant chemotherapy with 5-fluorouracil (5-FU), leucovorin (LCV), and oxaliplatin. Oral capecitabine may be substituted for intravenous 5-FU/LCV. In patients with metastatic disease, surgical evaluation should be conducted, especially in those with limited hepatic metastases. If the tumor is deemed unresectable, palliative chemotherapy with a 5-FU/

LCV regimen should be offered. Potential regimens include FOLFOX (5-FU/LCV and oxaliplatin), FOLFIRI (5-FU/LCV and irinotecan), CapeOX (capecitabine and oxaliplatin), 5-FU/LCV alone, and capecitabine alone. Biologic therapy with bevacizumab (with FOLFOX, FOLFIRI, or CapeOX), panitumumab (with FOLFOX or FOLFIRI), or cetuximab (FOLFIRI) may be added to standard regimens. KRAS is an important cell-signaling protein in the growth and progression of tumor cells. Malignancies with mutated KRAS, which occur in 40% of patients with CRC, are associated with poor response to epidermal growth factor receptor (EGFR) inhibitors, including cetuximab and panitumumab. This occurs since KRAS signaling happens downstream from EGFR. With progressive disease, regimens can be changed to another option with medications not already utilized.<sup>3</sup> In 2012, 2 new agents were approved for use as second-line therapy. Ziv-alibercept, a vascular endothelial growth factor receptor (VEGFR) 1 and 2 inhibitor, when combined with FOLFIRI in those who had failed a previous oxaliplatin-based regimen, had an improved OS of 1.4 months compared with those who received placebo (13.5 months vs 12.1 months,  $P = .003$ ).<sup>4</sup> Regorafenib, an oral multikinase inhibitor, demonstrated

an improved OS over placebo in patients who had failed standard therapy in the CORRECT trial (6.4 months vs 5 months,  $P = .005$ ).<sup>5</sup> Of note, even though this article will focus on colon cancer, patients with rectal cancers are also included in many of the clinical trials.

## Topoisomerase I Inhibitors

In stages III and IV CRC, traditional chemotherapy has been shown to improve OS. Irinotecan, a topoisomerase I inhibitor commonly used in the metastatic setting, is broken down into its active metabolite SN-38. When SN-38 binds to topoisomerase I, it prevents single-strand repair, which causes permanent single- and double-strand DNA breakage.<sup>6</sup> Two products in phase II and III trials, etirinotecan pegol (NKTR-102) and EZN-2208, are pegylated versions of irinotecan which delay clearance and prolong the half-life of SN-38.<sup>7,8</sup> Specifically, etirinotecan pegol is a pegylated prodrug of irinotecan, while EZN-2208 is the pegylated formulation of SN-38. In a phase I trial of 76 patients, including 17 patients with CRC, etirinotecan pegol was given at a maximum tolerated dose (MTD) of 115 mg/m<sup>2</sup> dose in patients treated on days 1, 8, and 15 in a 28-day cycle, and 145 mg/m<sup>2</sup> in patients treated once every 2 weeks or once every 3 weeks. Two patients with CRC had a partial response (PR), with 1 of those patients being unconfirmed by traditional response criteria. The dose-limiting toxicity (DLT) was grade 3 diarrhea in all dosing schemata.<sup>9</sup> The half-life of SN-38 was 50 days compared with only 12 to 47 hours with irinotecan studies.<sup>6,9</sup> EZN-2208 has been studied as a third-line treatment in 173 metastatic colorectal cancer (mCRC) patients who had previously failed 5-FU, oxaliplatin, and irinotecan. Patients with KRAS mutations received EZN-2208 at 9 mg/m<sup>2</sup> once daily on days 1, 8, and 15 of a 28-week cycle, while patients with KRAS wild-type received either EZN-2208 with cetuximab or irinotecan with cetuximab. No responses

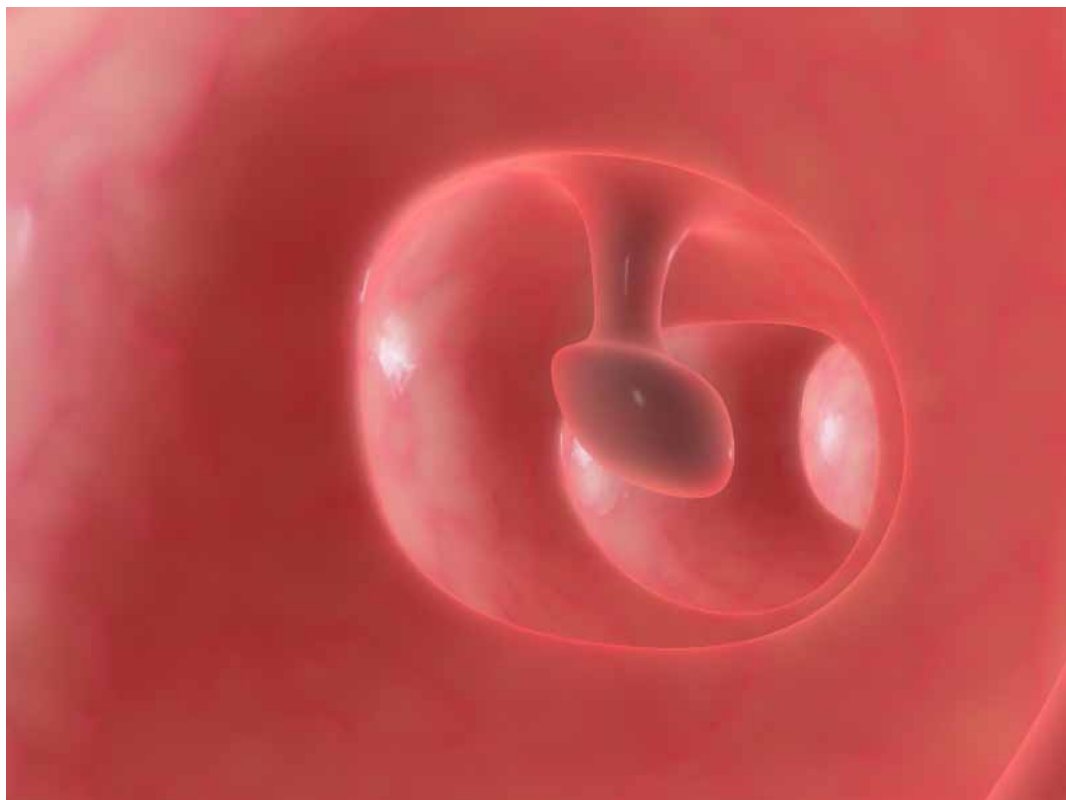
were seen with the first group who had received single-agent EZN-2208, but 9% of patients had a response to the second arm (EZN-2208 and cetuximab) and 14% had a response to the third arm (irinotecan and cetuximab). The most common adverse effects in all groups were gastrointestinal (GI).<sup>10</sup>

## TAS-102

TAS-102 consists of 2 components:  $\alpha, \alpha, \alpha$ -trifluorothymidine (FTD), the active agent, and 5-chloro-6-(2-iminopyrrolidin-1-yl) methyl-2,4 (1H,3H)-pyrimidinedione hydrochloride utilized to prevent first-pass metabolism and maintain therapeutic FTD concentrations with oral administration. FTD exerts its activity by inhibiting thymidylate synthase and inhibiting DNA transcription by incorporating into base pairs when phosphorylated. A phase II trial included 169 adult patients with mCRC who had failed  $\geq 2$  chemotherapy regimens, including 5-FU, irinotecan, and oxaliplatin. TAS-102 dosed at 35 mg/m<sup>2</sup> orally, twice daily or placebo, was given to patients on days 1 to 5 in a 28-day cycle. The median OS for the TAS-102 group was 9 months compared with 6.6 months for the placebo group ( $P = .001$ ). There was a median progression-free survival (PFS) of 1 month (2 months vs 1 month) for the TAS-102 group ( $P < .0001$ ). Only 1 patient in the TAS-102 group had a PR, but 43% of patients achieved stable disease (SD). Severe adverse events included bone marrow suppression, fatigue, diarrhea, and febrile neutropenia.<sup>11</sup> A phase III trial is under way to compare the OS and toxicity of TAS-102 versus placebo in patients with refractory mCRC.<sup>12</sup>

## ThermoDox

ThermoDox is a doxorubicin-based low temperature-sensitive liposome in phase II clinical trials for the treatment of recurrent or refractory unresectable liver metastases ( $\leq 4$  metastases with a diameter of 2-7 cm) in patients with CRC, along with radiofrequency ablation (RFA) compared with RFA alone.<sup>13</sup> Use of the nanoparticle ThermoDox with mild hyperthermia (41°C-42°C) should allow for doxorubicin to be delivered and released directly into the liver metastases and therefore avoid systemic distribution. Doxorubicin



Date Updated	Company/Sponsor	Product	Mechanism of Action	Indication(s)	Stage(s)	Licensee/Partner(s)	PDUFA Date
Sep 10, 2012	Bristol-Myers Squibb	Brivanib alaninate (BMS-582664)	VEGF Inhibitor	K-Ras wild type relapsed or refractory mCRC with cetuximab, irinotecan, or both	Phase II/III	MD Anderson Cancer Center/NCIC Clinical Trials Group	N/A
Nov 9, 2012	Syndax	Entinostat (MS-275)	HDAC Inhibitor	Relapsed/refractory mCRC	Phase II	NCI	N/A
Sep 12, 2012	Nektar Therapeutics	Etirinotecan pegol (NKTR-102)	Topoisomerase I Inhibitor	K-Ras mutant relapsed/refractory mCRC	Phase II/III	N/A	N/A
Sep 19, 2011	Enzon Pharmaceuticals, Inc	Firtecán pegol (EZN-2208)	Topoisomerase I Inhibitor	Relapsed/refractory mCRC ± cetuximab	Phase II	N/A	N/A
May 17, 2012	Gradalis, Inc	FANG	Immunomodulatory Vaccine	Operable mCRC with liver metastases, with adjuvant modified FOLFOX6	Phase II	N/A	N/A
Oct 26, 2012	GlobelImmune	GI-4000 vaccine	Immunomodulatory Vaccine	K-Ras mutant newly diagnosed mCRC	Phase II	Georgetown University	N/A
Sep 17, 2012	Gilead Sciences	GS-6624	Monoclonal Antibody	K-Ras mutant relapsed/refractory mCRC with FOLFIRI	Phase II	N/A	N/A
Oct 11, 2012	Biothera	Imprime PGG	Immunomodulatory Vaccine	K-Ras wild type relapsed/refractory mCRC with cetuximab	Phase III	N/A	N/A
May 14, 2012	GlaxoSmithKline	Lapatinib (Tykerb)	EGFR and HER2 Inhibitor	Relapsed/refractory mCRC with cetuximab	Phase I	Georgetown University	N/A
Jun 8, 2012	Genentech	Onartuzumab (Met-Mab)	Monoclonal Antibody	mCRC with FOLFOX and bevacizumab	Phase II	Sarah Cannon Research Institute	N/A
Nov 14, 2012	Eli Lilly and Company	Ramucirumab (IMC-1121B or LY3009806)	Monoclonal Antibody	Relapsed/refractory mCRC with FOLFIRI	Phase III	ImClone LLC	N/A
Feb 9, 2012	AstraZeneca	Rosuvastatin (Crestor)	Statin, HMG-CoA Reductase Inhibitor	Operable stage I or II CRC following surgery	Phase III	NSABP, NCI	N/A
Jan 31, 2012	Leiden Medical Center, NCI, Samsung Medical Center	Simvastatin (Zocor)	Statin, HMG-CoA Reductase Inhibitor	Relapsed/refractory mCRC with panitumumab, cetuximab, or XELIRI/FOLFIRI or K-Ras mutant relapsed/refractory mCRC with cetuximab and irinotecan	Phase II and Phase III	N/A	N/A
Nov 5, 2012	Onyx Pharmaceuticals, Bayer Healthcare	Sorafenib (BAY43-9006)	Multikinase Inhibitor	Relapsed/refractory mCRC with multiple different agents	Phase I and Phase II	NCI, Centre Val d'Aurelle – Paul Lamarque, University of Florida, Mayo Clinic, MD Anderson Cancer Center, etc	N/A
Sep 28, 2012	Taiho Pharmaceutical	TAS-102	Antimetabolite	Relapsed/refractory mCRC	Phase III	N/A	N/A
Jun 4, 2012	Celsion Corp	ThermoDox	Anthracycline, Low Temperature-Sensitive Liposome	Relapsed/refractory mCRC with unresectable liver metastases given with radio-frequency ablation	Phase II	N/A	N/A
Apr 12, 2012	Daiichi Sankyo Inc	Tivantinib (ARQ 197)	C-MET Inhibitor	Wild-type K-Ras relapsed/refractory mCRC	Phase I/II	N/A	N/A
Apr 26, 2012	Abbott Laboratories	Veliparib (ABT-888)	PARP Inhibitor	Relapsed/refractory mCRC along with temozolomide	Phase II	Georgetown University	N/A

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

given along with hyperthermia has been shown to potentially cause a synergistic effect by increasing chemotherapy penetration into the tumor.<sup>14</sup>

#### Ramucirumab

Tumor angiogenesis, a crucial mecha-

nism in cancer growth and metastasis, occurs as a result of interactions between VEGF and VEGFR. VEGF-A, an important component of tumor angiogenesis, endothelial proliferation, permeability, and survival, binds to both VEGFR-1 and VEGFR-2, which can be found

on tumor vasculature.<sup>15</sup> Ramucirumab is a human monoclonal antibody targeting VEGF, specifically blocking the interactions between all known VEGFs and VEGFR-2.<sup>15,16</sup> This interaction has been shown to inhibit angiogenesis and tumor growth in preclinical studies.<sup>15</sup>

Because ramucirumab actually blocks the binding to these receptors, it differs in mechanism from other VEGF-directed therapies already available.<sup>16</sup> A phase I study was completed in patients with advanced solid malignancies who were receiving escalating,

once-weekly doses of ramucirumab. Six of the 37 patients included in the study had CRC. Authors observed anti-tumor activity and antiangiogenic effects with varying doses. Two patients experienced dose-limiting toxicities (grade 3 hypertension and deep vein thrombosis) after receiving a dose of 16 mg/kg; therefore the MTD was set at 13 mg/kg.<sup>15</sup> The primary side effects observed with ramucirumab include hypertension, vascular thrombotic events, proteinuria, and bleeding.<sup>15,16</sup> A phase II study investigating if patients with mCRC have an improved PFS when treated with standard chemotherapy, standard chemotherapy plus ramucirumab, or standard chemotherapy plus icrucumab, a monoclonal antibody targeting VEGFR-1, is currently recruiting patients.<sup>17,18</sup> A phase III study currently recruiting patients will compare OS in mCRC patients treated with either ramucirumab plus FOLFIRI or FOLFIRI monotherapy.<sup>19</sup>

#### Brivanib

A new approach to intracellular signal blockade is noted with brivanib, a novel receptor tyrosine kinase inhibitor (TKI). In addition to VEGFR-2, which was previously discussed, fibroblast growth factor-1 (FGF-1) and -2 (FGF-2) plays a role in both angiogenesis and tumorigenesis. In order to combat the resistance seen with bevacizumab, an FDA-approved VEGF-2 inhibitor, it has been theorized that the FGF pathway should be targeted. Brivanib works by targeting FGF and VEGF signaling simultaneously.<sup>20</sup> Brivanib alaninate is an oral L-alanine ester pro-drug which is hydrolyzed into its active form, brivanib.<sup>20,21</sup> Preclinical studies indicate that brivanib has antiangiogenic and antitumor effects in colon cancer.<sup>20</sup> In 1 pharmacokinetic study of only 4 patients, brivanib was well tolerated, with fatigue occurring in all patients and the second-most common adverse events being GI (nausea, diarrhea, and constipation).<sup>21</sup> Advantages of this new agent include that it is taken orally on a daily basis. A phase I dose-escalation study evaluating brivanib plus cetuximab in advanced GI malignancies included 59 participants with CRC.<sup>20</sup> Six patients received 320 mg, 5 patients received 600 mg, and 51 patients received 800 mg of brivanib. Overall, brivanib was well tolerated in this study; however, 4 patients in the 800-mg group discontinued the study due to drug-related toxicities, including sepsis, aspartate aminotransferase elevations, dehydration, and angioedema. One patient died due to sepsis from rectal perforation, which was possibly due to brivanib.

The majority of adverse effects were grade 1/2 and the most frequently reported grade 3/4 adverse effects were fatigue and elevated hepatic transaminases. Approximately 10% of patients in the 800-mg group experienced grade 1/2 palmar-plantar erythrodysesthesia.<sup>20</sup> A randomized phase III study is under way to evaluate whether or not brivanib plus cetuximab is more effective than cetuximab monotherapy in treating patients with mCRC.<sup>22</sup>

#### Tivantinib

Several cancers have been linked to mutations in the mesenchymal-epithelial transition (MET) gene including CRC.<sup>23-25</sup> Gene mutations, gene amplifications, and protein overexpression are a few ways c-MET receptor tyrosine kinase can be activated. Activation of c-Met can trigger several oncogenic processes, including tumor cell proliferation, migration, invasion, angiogenesis, development of metastases, and protection from apoptosis, thus leading to poorer clinical outcomes and drug resistance.<sup>25</sup> The c-MET inhibitor, tivantinib, is an orally administered TKI which is selective for hepatocyte growth factor receptor (HGFR). HGFR is a product of the MET gene that can induce cell growth and reduce apopto-

**Similar to most malignancies, the future of colon cancer research is focused on targeted and personalized therapy, with VEGF being the most commonly targeted pathway in current clinical trials.**

sis, among other detrimental effects.<sup>23</sup> A phase I dose escalation study in 79 patients with metastatic solid tumors did not determine an MTD; however, it was concluded that 360 mg twice a day was well tolerated, with patients experiencing mild to moderate toxicities. In this study, 4% of patients achieved a PR while approximately 50% maintained SD for a median of about 20 weeks.<sup>26</sup> A phase I/II study evaluating tivantinib in

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CRC is currently ongoing. The phase I part of the study will determine the efficacy, safety, and recommended dose of tivantinib in combination with irinotecan and cetuximab. The phase II part will be a randomized, double-blind, placebo-controlled study to determine safety and efficacy of tivantinib plus irinotecan and cetuximab by measuring time to PFS in subjects with wild-type KRAS CRC.<sup>27</sup>

#### Ornatuzumab

The monoclonal antibody, ornatuzumab, another agent that targets HGFR, is a monovalent HGF antagonist antibody against MET.<sup>23</sup> No phase II or III trials have been completed in patients with CRC; however, preliminary results from a phase II trial in patients with small cell lung cancer receiving either ornatuzumab plus erlotinib or erlotinib alone demonstrated that only patients who overexpress HGFR may benefit. Patients with c-MET negative tumors had worse OS when compared with placebo.<sup>28</sup> Investigators are actively recruiting for a randomized, double-blind placebo-controlled trial evaluating FOLFOX plus bevacizumab and ornatuzumab or placebo as first-line treatment in mCRC.<sup>29</sup>

#### Lapatinib

Lapatinib is an oral TKI for human epidermal growth factor 2 (HER2) and EGFR currently approved for treatment in HER2+ metastatic breast cancer after failure of trastuzumab. HER2 and EGFR are enzymes essential for tumor growth and development. HER2 overexpression is only found in a small fraction of colon cancer patients, but patients with wild-type KRAS have been shown to respond to EGFR inhibitors. Adults with advanced mCRC or mCRC with progression during or within 6 months of chemotherapy with 5-FU, oxaliplatin, or irinotecan were eligible for a phase II study in which lapatinib was given at 1250 mg orally daily and capecitabine 2000 mg/m<sup>2</sup> orally twice daily on days 1 to 14 of a 21-day cycle. Enrollment was stopped at 29 patients due to an ORR of 0%. The incidence of SD at the time of study termination was 41.4%, with the most severe toxicities being palmar-plantar

erythrodysesthesia, GI, and fatigue.<sup>30</sup> Even though this study did not show a benefit with lapatinib, there is a phase I trial recruiting patients with CRC, lung, or head and neck cancer looking at the MTD and DLT of cetuximab and lapatinib together.<sup>31</sup>

#### Entinostat

Histone deacetylases (HDACs) are enzymes that cause the binding of DNA phosphate group to histones and therefore prevent DNA transcription. Inhibition of this process causes a buildup of acetyl groups, leading to transcription factor abnormalities and, ultimately, cell apoptosis. Numerous cancers are associated with abnormalities in the histone acetylase and HDAC enzymes.<sup>32</sup> Entinostat (MS-275 or SNDX-275) is an oral HDAC inhibitor being studied in a phase II trial along with azacitidine for patients with mCRC who have failed  $\geq 2$  previous regimens.<sup>33</sup> In a phase I study, 4 out of the 27 patients treated with entinostat had mCRC. The MTD was 4 mg/m<sup>2</sup> orally once daily on days 1, 8, and 15 of a 28-day cycle, with the DLT being both asthenia and hypophosphatemia. One patient with colon cancer obtained SD.<sup>32</sup>

#### Sorafenib

Sorafenib, an oral multikinase inhibitor, is currently FDA approved for the treatment of unresectable hepatocellular and renal cell carcinoma. Sorafenib's mechanisms of action include inhibition of BRAF, VEGF-1/-2/-3, platelet-derived growth factor  $\beta$ , c-KIT, FLT-3 (fms-like tyrosine kinase receptor-3), and RET ("rearranged during transfection") tyrosine kinases. BRAF, a Raf kinase, is essential for activating cancer cell growth, division, and maturation.<sup>34</sup> Currently, multiple phase I and II trials are being conducted in patients with relapsed or refractory mCRC, utilizing sorafenib along with standard second-line agents.<sup>35</sup> Twenty-six patients with mCRC were included in a Phase I trial that combined sorafenib along with 2 different 5-FU/LCV infusion schedules, the Mayo Clinic and Roswell Park regimens. Two patients diagnosed with colon cancer achieved a PR and 42%

(continued on page 36)

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(continued from page 34)

achieved SD, but the original diagnoses for these patients achieving SD were not defined. Severe adverse effects occurred in the majority of patients (55%), with the most common organ systems affected being the GI and hepatic systems.<sup>34</sup>

#### Veliparib (ABT-888)

Veliparib inhibits PARP-1 and -2 enzymes (poly[ADP-ribose] polymerase), which are necessary for repairing DNA. When combined with alkylating agents, such as cyclophosphamide, PARP inhibitors enhance the DNA damage caused by the alkylating agents. Forty-seven patients with mCRC who had progressed on “all” standard therapies received temozolomide, an alkylating agent, at 150 mg/m<sup>2</sup> orally once daily on days 1 to 5 and veliparib 40 mg orally twice daily on days 1 to 7 of a 28-day cycle until progression. Five percent of patients obtained a PR and 18% had SD. The most severe adverse effect was myelosuppression, which only occurred in 11% of patients.<sup>36</sup> Two clinical trials are actively recruiting participants: a phase II trial utilizing the temozolomide/veliparib regimen and a phase I trial using veliparib, oxaliplatin, and capecitabine in patients with treatment-naïve or relapsed mCRC along with other predefined malignancies.<sup>37</sup>

#### HMG CoA Reductase Inhibitors

A class of anti-lipid agents called 3-hydroxy-3-methylglutaryl (HMG) CoA reductase inhibitors, also known as statins, is thought to have anti-neoplastic effects in colon cancer by inducing apoptosis, inhibiting angiogenesis and cell proliferation, and decreasing metastatic capacity.<sup>38</sup> A phase II study evaluating the addition of 40 mg simvastatin daily to FOLFIRI treatment in mCRC in 49 patients demonstrated an ORR of 46.9% (95% confidence interval, 31.0-58.8) by intent-to-treat analysis.<sup>39</sup> Currently, there are 3 studies evaluating simvastatin added to other regimens in mCRC open to accrual.<sup>40</sup> A phase II study closed to accrual is ongoing to determine if conventional cetuximab treatment with 40 mg simvastatin added is effective in mCRC patients with KRAS mutation.<sup>41</sup> A randomized phase III study is currently recruiting patients to determine how the HMG reductase inhibitor, rosuvastatin, compares with placebo in treating patients with stage I or II colon cancer removed by surgery.<sup>42</sup>

#### Monoclonal Antibodies

The lysol oxidase family of proteins

contain a conserved catalytic region and are thought to play a role in cancer progression.<sup>43</sup> One of the 5 LOX proteins, LOX-like 2 (LOXL2), is an extracellular matrix which has been shown to play a role in several disease states, including colon cancer.<sup>43,44</sup> GS-6624, formerly AB0024, is a humanized monoclonal antibody that targets LOXL-2.<sup>45</sup> A phase I study was completed in March 2012 that investigated the safety, tolerability, pharmacokinetics, and pharmacodynamics of AB0024 in adult patients with advanced malignant solid tumors.<sup>46</sup> A phase II randomized, double-blind, placebo-controlled study is currently recruiting patients with KRAS mutant mCRC to determine the efficacy and safety of GS-6624 when combined with FOLFIRI as second-line treatment. To be included in the study, patients had to have had disease progression after first-line treatment with an oxaliplatin and 5-FU-containing regimen. The primary outcome of this study is PFS.<sup>47</sup>

#### Imprime PGG

Currently undergoing phase III trials for KRAS wild type mCRC,<sup>48</sup> Imprime PGG is a beta-glucan polymer that sensitizes neutrophils to target cancer cells already treated with a monoclonal antibody. This synergistic activity is thought to improve the response to traditional cancer therapies. Imprime PGG has been given along with cetuximab, a monoclonal antibody which targets EGFR. Twenty-two patients with KRAS wild-type CRC were enrolled in a phase Ib/II trial and received weekly Imprime PGG with cetuximab and irinotecan or Imprime PGG with cetuximab alone. Patients who received cetuximab alone with Imprime PGG had a 24% ORR and 38% obtained SD. Time to progression was found to be 4 months. Adverse effects were similar to those found with cetuximab administration.<sup>49</sup>

#### FANG Vaccine

This vaccine consists of autologous tumor cells from the patient and a plasmid expressing growth macrophage colony stimulating factor (GM-CSF) and bifunctional short hairpin RNA<sup>furin</sup> (bi-shRNA<sup>furin</sup>). GM-CSF induces growth and production of dendritic cells, or essential antigen-presenting cells, in the bone marrow. Bi-shRNA<sup>furin</sup> inhibits production of furin, an enzyme that transforms precursor proteins into active proteins. The specific target for Bi-shRNA<sup>furin</sup> is transforming growth factor  $\beta$  1 and 2 (TGF $\beta$ ). TGF $\beta$  is associated with both normal and tumor cell growth, with the overexpression of this

protein often being linked to cancer progression. Also, TGF $\beta$  causes immune suppression specifically inhibiting GM-CSF, making all components essential for vaccine response. According to phase I data, 6 patients with colon cancer received this vaccine and all patients obtained SD after 3 to 5 vaccine administrations.<sup>50</sup> Further studies are planning to utilize the FANG vaccine for 5 to 12 doses in patients following curative resection of liver metastases caused by CRC, along with 6 cycles of modified FOLFOX6 chemotherapy.<sup>51</sup>

#### GI-4000 Vaccine

GI-4000 is a patient-specific vaccine for the treatment of mCRC along with standard chemotherapy treatment. The specific mutation of KRAS is identified in each patient and the appropriate targeted molecular immunogens (targomogs) are created out of heat-killed recombinant *S cerevisiae* yeast. Use of GI-4000 activates T cells, which cause selective killing of mutant KRAS cells or tumor cells.<sup>52</sup> FOLFOX or FOLFIRI chemotherapy, along with adjuvant and maintenance bevacizumab, is being given along with GI-4000 in all patients in a current phase II trial. GI-4000 is given prior to starting chemotherapy, then administered 7 days after each chemotherapy cycle begins (FOLFOX/FOLFIRI) for up to 8 cycles. During bevacizumab maintenance, GI-4000 is to be given every 2 weeks. Currently, patients may be enrolled prior to starting chemotherapy or prior to starting maintenance bevacizumab.<sup>53</sup>

#### Conclusion

Similar to most malignancies, the future of colon cancer research is focused on targeted and personalized therapy, with VEGF being the most commonly targeted pathway in current clinical trials. With the utilization of targeted therapy, the focus of treatment becomes the identification of patients who will benefit from this therapy. This is already seen in current practices, with the use of KRAS testing becoming the standard of care prior to initiating treatment for mCRC and utilization of EGFR inhibitors. Other pathways which are utilized or have been studied in other malignancies are also being studied in CRC, including HDAC, c-MET, and PARP. Along with traditional chemotherapy agents, new agents NKTR-102, EZN-2208, and ThermoDox are being created to improve the pharmacokinetics and delivery of the drug, which will hopefully improve both clinical benefit and patient tolerability. Immunomodulatory pathways, previously not found

to be beneficial, have shown some promise in phase I and II trials. Currently, the main concern from a managed care perspective is the cost-benefit ratio of these medications. With 2 new agents approved in 2012, with only a 1.4-month OS benefit, the question that arises is the cost, both economic and quality of life. Past pharmacoeconomic studies have looked at the use of currently approved targeted therapies and the incremental cost-effectiveness ratio (ICER) per discounted life-year. Based upon 2008 Medicare reimbursements, the ICER in \$/year, or the cost of saving a life-year, with targeted therapies (bevacizumab or cetuximab) added to conventional chemotherapy, was \$170,896 per year compared with \$102,336 per year for conventional chemotherapy.<sup>54</sup> With the approval of more targeted therapies, pharmacoeconomic studies are pivotal in assessing the effects on future healthcare costs. Future

**With the approval of more targeted therapies, pharmacoeconomic studies are pivotal in assessing the effects on future healthcare costs.**

QOL studies would be also useful to demonstrate if the response or small survival gains are worth the toxicities, especially in non-curable diseases like CRC. **EBO**

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# DOXIL<sup>®</sup>

(doxorubicin HCl liposome injection)

ORDER DOXIL<sup>®</sup> THROUGH YOUR AUTHORIZED DISTRIBUTOR

## INDICATIONS

- DOXIL<sup>®</sup> is indicated for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy
- DOXIL<sup>®</sup> in combination with VELCADE<sup>®</sup> (bortezomib) is indicated for the treatment of patients with multiple myeloma who have not previously received VELCADE and have received at least one prior therapy

## IMPORTANT SAFETY INFORMATION

### BOXED WARNINGS

Cardiotoxicity, infusion reaction, myelosuppression, liver impairment, substitution

- The use of DOXIL<sup>®</sup> may lead to cardiac toxicity. Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m<sup>2</sup>
  - Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dose
  - Cardiac toxicity may also occur at lower cumulative doses (400 mg/m<sup>2</sup>) in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy
- Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with DOXIL<sup>®</sup>. In most patients, these reactions have resolved within several hours to a day once the infusion is terminated. In some patients, reactions resolved with slowing of the infusion rate
  - Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have occurred. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use
  - The initial rate of infusion should be 1 mg/min to minimize the risk of infusion reactions

- Severe myelosuppression may occur
- DOXIL<sup>®</sup> dosage should be reduced in patients with impaired hepatic function
- Accidental substitution has resulted in severe side effects. Do not substitute for doxorubicin HCl on a mg per mg basis

## CONTRAINDICATIONS

- Patients with a history of hypersensitivity reactions to a conventional doxorubicin formulation or the components of DOXIL<sup>®</sup>

## ADDITIONAL SAFETY INFORMATION

- Cardiac function should be carefully monitored
  - Congestive heart failure or cardiomyopathy may occur after discontinuation of anthracycline therapy
  - For patients with a history of cardiovascular disease, or if the results of cardiac monitoring indicate possible cardiac injury, the benefit of therapy must be weighed against the risk of myocardial injury
  - In the randomized multiple myeloma study, 25 patients (8%) in the VELCADE arm and 42 patients (13%) in the DOXIL<sup>®</sup> plus VELCADE arm experienced left ventricular ejection fraction decrease (defined as absolute decrease  $\geq$ 15% over baseline or a  $\geq$ 5% decrease below institutional lower limit of normal)
- Myelosuppression may occur; frequently monitor complete blood count (including platelet count), at least prior to each dose of DOXIL<sup>®</sup>
  - In patients with recurrent ovarian cancer, hematologic toxicity (based on platelet count or absolute neutrophil count) may require dose reduction or delay in administration of DOXIL<sup>®</sup>
  - In patients with multiple myeloma, hematologic toxicity (based on platelet count, absolute neutrophil count, hemoglobin level, or neutropenia with fever) may require dose reduction, delay in administration, or suspension of DOXIL<sup>®</sup> and/or VELCADE



# DOXIL<sup>®</sup> Is Now Available.

## We Are COMMITTED

long-term to ensuring a reliable supply of DOXIL<sup>®</sup>.

## Prescribe With CONFIDENCE.

The brand you've long relied on remains an important therapeutic option for you and your patients.

- Persistent severe myelosuppression may result in superinfection, neutropenic fever, or hemorrhage
- Sepsis occurring during neutropenia has resulted in discontinuation of treatment and, in rare cases, death
- DOXIL<sup>®</sup> may potentiate the toxicity of other anticancer therapies, especially hematologic toxicities, when used in combination with other therapies that suppress bone marrow
- Hand-foot syndrome (HFS) may occur during therapy with DOXIL<sup>®</sup>
  - Based on HFS toxicity grade, dose reduction, delay in administration, or discontinuation of DOXIL<sup>®</sup> may be required
  - HFS was generally observed after 2 to 3 cycles of treatment, but may occur earlier
    - The reaction was mild in most patients, resolving in 1 to 2 weeks
    - The reaction can be severe and debilitating in some patients, resulting in discontinuation of therapy
- DOXIL<sup>®</sup> is an irritant, not a vesicant; use precautions to avoid extravasation
- DOXIL<sup>®</sup> can cause fetal harm when used during pregnancy
- Because of the potential for serious adverse reactions in nursing infants, discontinue nursing during treatment with DOXIL<sup>®</sup>.
- Recall reaction has occurred with DOXIL<sup>®</sup> administration after radiotherapy
- DOXIL<sup>®</sup> may interact with drugs known to interact with the conventional formulation of doxorubicin HCl
- In patients with recurrent ovarian cancer, the most common all-grade adverse reactions (ARs)  $\geq 20\%$  (DOXIL<sup>®</sup> vs topotecan, respectively) included: asthenia (40% vs 51%), fever (21% vs 31%), nausea (46% vs 63%), stomatitis (41% vs 15%), vomiting (33% vs 44%), diarrhea (21% vs 35%), anorexia (20% vs 22%), dyspnea (15% vs 23%), HFS (51% vs 1%), and rash (29% vs 12%)
  - In addition, 19% vs 52.3% reported alopecia (all grades)
  - Grade 3/4 hematologic ARs reported in  $\geq 5\%$  (DOXIL<sup>®</sup> vs topotecan, respectively) were neutropenia (12% vs 76%) and anemia (6% vs 29%)
- In patients with multiple myeloma, the most common all-grade ARs  $\geq 20\%$  (DOXIL<sup>®</sup> plus VELCADE vs VELCADE, respectively) included: neutropenia (36% vs 22%), thrombocytopenia (33% vs 28%), anemia (25% vs 21%), fatigue (36% vs 28%), pyrexia (31% vs 22%), asthenia (22% vs 18%), nausea (48% vs 40%), diarrhea (46% vs 39%), vomiting (32% vs 22%), constipation (31% vs 31%), mucositis/stomatitis (20% vs 5%), peripheral neuropathy (42% vs 45%), neuralgia (17% vs 20%), and rash (22% vs 18%)
  - In addition, 19% vs  $<1\%$  reported HFS

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

Janssen Products, LP

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**janssen**  
PHARMACEUTICAL COMPANIES  
OF Johnson & Johnson

K08D121023

## DOXIL®

(doxorubicin HCl liposome injection)  
for intravenous infusion

**BRIEF SUMMARY. Please see Full Prescribing Information.**

### **WARNING: INFUSION REACTIONS, MYELOSUPPRESSION, CARDIOTOXICITY, LIVER IMPAIRMENT, ACCIDENTAL SUBSTITUTION**

1. The use of DOXIL (doxorubicin HCl liposome injection) may lead to cardiac toxicity. Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m<sup>2</sup>. In a clinical study in patients with advanced breast cancer, 250 patients received DOXIL at a starting dose of 50 mg/m<sup>2</sup> every 4 weeks. At all cumulative anthracycline doses between 450-500 mg/m<sup>2</sup> or between 500-550 mg/m<sup>2</sup>, the risk of cardiac toxicity for patients treated with DOXIL was 11%. Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. Cardiac toxicity may also occur at lower cumulative doses in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy [see Warnings and Precautions]. 2. Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with DOXIL. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction has resolved with slowing of the infusion rate. Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. DOXIL should be administered at an initial rate of 1 mg/min to minimize the risk of infusion reactions [see Warnings and Precautions]. 3. Severe myelosuppression may occur [see Warnings and Precautions]. 4. Dosage should be reduced in patients with impaired hepatic function [see Full Prescribing Information]. 5. Accidental substitution of DOXIL for doxorubicin HCl has resulted in severe side effects. DOXIL should not be substituted for doxorubicin HCl on a mg per mg basis [see Full Prescribing Information].

**INDICATIONS AND USAGE: Ovarian Cancer:** DOXIL (doxorubicin HCl liposome injection) is indicated for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy. **Multiple Myeloma:** DOXIL in combination with bortezomib is indicated for the treatment of patients with multiple myeloma who have not previously received bortezomib and have received at least one prior therapy.

**CONTRAINDICATIONS:** DOXIL (doxorubicin HCl liposome injection) is contraindicated in patients who have a history of hypersensitivity reactions to a conventional formulation of doxorubicin HCl or the components of DOXIL [see Warnings and Precautions].

**WARNINGS AND PRECAUTIONS: Cardiac Toxicity:** Special attention must be given to the risk of myocardial damage from cumulative doses of doxorubicin HCl. Acute left ventricular failure may occur with doxorubicin, particularly in patients who have received a total cumulative dosage of doxorubicin exceeding the currently recommended limit of 550 mg/m<sup>2</sup>. Lower (400 mg/m<sup>2</sup>) doses appear to cause heart failure in patients who have received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide. Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. Congestive heart failure or cardiomyopathy may be encountered after discontinuation of anthracycline therapy. Patients with a history of cardiovascular disease should be administered DOXIL only when the potential benefit of treatment outweighs the risk. Cardiac function should be carefully monitored in patients treated with DOXIL. The most definitive test for anthracycline myocardial injury is endomyocardial biopsy. Other methods, such as echocardiography or multigated radionuclide scans, have been used to monitor cardiac function during anthracycline therapy. Any of these methods should be employed to monitor potential cardiac toxicity in patients treated with DOXIL. If these test results indicate possible cardiac injury associated with DOXIL therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury. In a clinical study in patients with advanced breast cancer, 250 patients received DOXIL at starting dose of 50 mg/m<sup>2</sup> every 4 weeks. At all cumulative anthracycline doses between 450-500 mg/m<sup>2</sup>, or between 500-550 mg/m<sup>2</sup>, the risk of cardiac toxicity for patients treated with DOXIL was 11%. In this study, cardiotoxicity was defined as a decrease of >20% from baseline if the resting left ventricular ejection fraction (LVEF) remained in the normal range, or a decrease of >10% if the resting LVEF became abnormal (less than the institutional lower limit of normal). The data on left ventricular ejection fraction (LVEF) defined cardiotoxicity and congestive heart failure (CHF) are in the table below.

**Table 1: Number of Patients With Advanced Breast Cancer**

	DOXIL (n=250)
Patients who Developed Cardiotoxicity (LVEF Defined)	10
Cardiotoxicity (With Signs & Symptoms of CHF)	0
Cardiotoxicity (no Signs & Symptoms of CHF)	10
Patients With Signs and Symptoms of CHF Only	2

In the randomized multiple myeloma study, the incidence of heart failure events (ventricular dysfunction, cardiac failure, right ventricular failure, congestive cardiac failure, chronic cardiac failure, acute pulmonary edema and pulmonary edema) was similar in the DOXIL+bortezomib group and the bortezomib monotherapy group, 3% in each group. LVEF decrease was defined as an absolute decrease of ≥ 15% over baseline or a ≥ 5% decrease below the institutional lower limit of normal. Based on this definition, 25 patients in the bortezomib arm (8%) and 42 patients in the DOXIL+bortezomib arm (13%) experienced a reduction in LVEF.

**Infusion Reactions:** Acute infusion-related reactions were reported in 7.1% of patients treated with DOXIL in the randomized ovarian cancer study. These reactions were characterized by one or more of the following symptoms: flushing, shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and hypotension. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction resolved when the rate of infusion was slowed. In this study, two patients treated with DOXIL (0.8%) discontinued due to infusion-related reactions. In clinical studies, six patients with AIDS-related Kaposi's sarcoma (0.9%) and 13 (1.7%) solid tumor patients discontinued DOXIL therapy because of infusion-related reactions. Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. The majority of infusion-related events occurred during the first infusion. Similar reactions have not been reported with conventional doxorubicin and they presumably represent a reaction to the DOXIL liposomes or one of its surface components. The initial rate of infusion should be 1 mg/min to help minimize the risk of infusion reactions [see Full Prescribing Information].

**Myelosuppression:** Because of the potential for bone marrow suppression, careful hematologic monitoring is required during use of DOXIL, including white blood cell, neutrophil, platelet counts, and Hgb/Hct. With the recommended dosage schedule, leukopenia is usually transient. Hematologic toxicity may require dose reduction or delay or suspension of DOXIL therapy. Persistent severe myelosuppression may result in superinfection, neutropenic fever, or hemorrhage. Development of sepsis in the setting of neutropenia has resulted in discontinuation of treatment and, in rare cases, death. DOXIL may potentiate the toxicity of other anticancer therapies. In particular, hematologic toxicity may be more severe when DOXIL is administered in combination with other agents that cause bone marrow suppression. In patients with relapsed ovarian cancer, myelosuppression was generally moderate and reversible. In the three single-arm studies, anemia was the most common hematologic adverse reaction (52.6%), followed by leukopenia (WBC <4,000 mm<sup>3</sup>; 42.2%), thrombocytopenia (24.2%), and neutropenia (ANC <1,000; 19.0%). In the randomized study, anemia was the most common hematologic adverse reaction (40.2%), followed by leukopenia (WBC <4,000 mm<sup>3</sup>; 36.8%), neutropenia (ANC <1,000; 35.1%), and thrombocytopenia (13.0%) [see Adverse Reactions]. In patients with relapsed ovarian cancer, 4.6% received G-CSF (or GM-CSF) to support their blood counts [see Full Prescribing Information]. For patients with AIDS-related Kaposi's sarcoma who often present with baseline myelosuppression due to such factors as their HIV disease or concomitant medications, myelosuppression appears to be the dose-limiting adverse reaction at the recommended dose of 20 mg/m<sup>2</sup> [see Adverse Reactions]. Leukopenia is the most common adverse reaction experienced in this population; anemia and thrombocytopenia can also be expected. Sepsis occurred in 5% of patients; for 0.7% of patients the event was considered possibly or probably related to DOXIL. Eleven patients (1.6%) discontinued study because of bone marrow suppression or neutropenia. Table 10 presents data on myelosuppression in patients with multiple myeloma receiving DOXIL and bortezomib in combination [see Adverse Reactions].

## DOXIL® (doxorubicin HCl liposome injection)

**Hand-Foot Syndrome (HFS):** In the randomized ovarian cancer study, 50.6% of patients treated with DOXIL at 50 mg/m<sup>2</sup> every 4 weeks experienced HFS (developed palmar-plantar skin eruptions characterized by swelling, pain, erythema and, for some patients, desquamation of the skin on the hands and the feet), with 23.8% of the patients reporting HFS Grade 3 or 4 events. Ten subjects (4.2%) discontinued treatment due to HFS or other skin toxicity. HFS toxicity grades are described in *Dosage and Administration* section [see Full Prescribing Information]. Among 705 patients with AIDS-related Kaposi's sarcoma treated with DOXIL at 20 mg/m<sup>2</sup> every 2 weeks, 24 (3.4%) developed HFS, with 3 (0.9%) discontinuing. In the randomized multiple myeloma study, 19% of patients treated with DOXIL at 30 mg/m<sup>2</sup> every three weeks experienced HFS. HFS was generally observed after 2 or 3 cycles of treatment but may occur earlier. In most patients the reaction is mild and resolves in one to two weeks so that prolonged delay of therapy need not occur. However, dose modification may be required to manage HFS [see Full Prescribing Information]. The reaction can be severe and debilitating in some patients and may require discontinuation of treatment.

**Radiation Recall Reaction:** Recall reaction has occurred with DOXIL administration after radiotherapy.

**Fetal Mortality: Pregnancy Category D:** DOXIL can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If DOXIL is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. If pregnancy occurs in the first few months following treatment with DOXIL, the prolonged half-life of the drug must be considered. Women of childbearing potential should be advised to avoid pregnancy during treatment with Doxil. [see Full Prescribing Information].

**Toxicity Potentiation:** The doxorubicin in DOXIL may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with the conventional formulation of doxorubicin HCl. Radiation-induced toxicity to the myocardium, mucosae, skin, and liver have been reported to be increased by the administration of doxorubicin HCl.

**Monitoring: Laboratory Tests:** Complete blood counts, including platelet counts, should be obtained frequently and at a minimum prior to each dose of DOXIL [see Warnings and Precautions].

**ADVERSE REACTIONS: Overall Adverse Reactions Profile:** The following adverse reactions are discussed in more detail in other sections of the labeling. • Cardiac Toxicity [see Warnings and Precautions] • Infusion reactions [see Warnings and Precautions] • Myelosuppression [see Warnings and Precautions] • Hand-Foot syndrome [see Warnings and Precautions]

The most common adverse reactions observed with DOXIL are asthenia, fatigue, fever, nausea, stomatitis, vomiting, diarrhea, constipation, anorexia, hand-foot syndrome, rash and neutropenia, thrombocytopenia and anemia. The most common serious adverse reactions observed with DOXIL are described in Section *Adverse Reactions in Clinical Trials*. The safety data described below reflect exposure to DOXIL in 1310 patients including: 239 patients with ovarian cancer, 753 patients with AIDS-related Kaposi's sarcoma and 318 patients with multiple myeloma.

**Adverse Reactions in Clinical Trials:** Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates on other clinical trials and may not reflect the rates observed in clinical practice. The following tables present adverse reactions from clinical trials of DOXIL in ovarian cancer, AIDS-Related Kaposi's sarcoma, and multiple myeloma.

**Patients With Ovarian Cancer:** The safety data described below are from 239 patients with ovarian cancer treated with DOXIL (doxorubicin HCl liposome injection) at 50 mg/m<sup>2</sup> once every 4 weeks for a minimum of 4 courses in a randomized, multicenter, open-label study. In this study, patients received DOXIL for a median number of 98.0 days (range 1-785 days). The population studied was 27-87 years of age, 91% Caucasian, 6% Black and 3% Hispanic and other. Table 2 presents the hematologic adverse reactions from the randomized study of DOXIL compared to topotecan.

**Table 2: Ovarian Cancer Randomized Study Hematology Data Reported in Patients With Ovarian Cancer**

	DOXIL Patients (n = 239)	Topotecan Patients (n = 235)
Neutropenia		
500 - <1000/mm <sup>3</sup>	19 (7.9%)	33 (14.0%)
<500/mm <sup>3</sup>	10 (4.2%)	146 (62.1%)
Anemia		
6.5 - <8 g/dL	13 (5.4%)	59 (25.1%)
<6.5 g/dL	1 (0.4%)	10 (4.3%)
Thrombocytopenia		
10,000 - <50,000/mm <sup>3</sup>	3 (1.3%)	40 (17.0%)
<10,000/mm <sup>3</sup>	0 (0.0%)	40 (17.0%)

Table 3 presents a comparative profile of the non-hematologic adverse reactions from the randomized study of DOXIL compared to topotecan.

**Table 3: Ovarian Cancer Randomized Study**

Non-Hematologic Adverse Reaction 10% or Greater	DOXIL (%) treated (n = 239)		Topotecan (%) treated (n = 235)	
	All grades	Grades 3-4	All grades	Grades 3-4
<b>Body as a Whole</b>				
Asthenia	40.2	7.1	51.5	8.1
Fever	21.3	0.8	30.6	5.5
Mucous Membrane Disorder	14.2	3.8	3.4	0
Back Pain	11.7	1.7	10.2	0.9
Infection	11.7	2.1	6.4	0.9
Headache	10.5	0.8	14.9	0
<b>Digestive</b>				
Nausea	46.0	5.4	63.0	8.1
Stomatitis	41.4	8.3	15.3	0.4
Vomiting	32.6	7.9	43.8	9.8
Diarrhea	20.9	2.5	34.9	4.2
Anorexia	20.1	2.5	21.7	1.3
Dyspepsia	12.1	0.8	14.0	0
<b>Nervous</b>				
Dizziness	4.2	0	10.2	0
<b>Respiratory</b>				
Pharyngitis	15.9	0	17.9	0.4
Dyspnea	15.1	4.1	23.4	4.3
Cough increased	9.6	0	11.5	0
<b>Skin and Appendages</b>				
Hand-foot syndrome	50.6	23.8	0.9	0
Rash	28.5	4.2	12.3	0.4
Alopecia	19.2	N/A	52.3	N/A

The following additional adverse reactions (not in table) were observed in patients with ovarian cancer with doses administered every four weeks.

Incidence 1% to 10%: **Cardiovascular:** vasodilation, tachycardia, deep thrombophlebitis, hypotension, cardiac arrest. **Digestive:** oral moniliasis, mouth ulceration, esophagitis, dysphagia, rectal bleeding, ileus. **Hemic and Lymphatic:** ecchymosis. **Metabolic and Nutritional:** dehydration, weight loss, hyperbilirubinemia, hypokalemia, hypercalcemia, hyponatremia. **Nervous:** somnolence, dizziness, depression. **Respiratory:** rhinitis, pneumonia, sinusitis, epistaxis. **Skin and Appendages:** pruritus, skin discoloration, vesiculobullous rash, maculopapular rash, exfoliative dermatitis, herpes zoster, dry skin, herpes simplex, fungal dermatitis, furunculosis, acne. **Special Senses:** conjunctivitis, taste perversion, dry eyes. **Urinary:** urinary tract infection, hematuria, vaginal moniliasis.

**Patients With Multiple Myeloma:** The safety data below are from 318 patients treated with DOXIL (30 mg/m<sup>2</sup> as a 1-hr i.v. infusion) administered on day 4 following bortezomib (1.3 mg/m<sup>2</sup> i.v. bolus on days 1, 4, 8 and 11) every three weeks, in a randomized, open-label, multicenter study. In this study, patients in the DOXIL + bortezomib combination group were treated for a median number of 138 days (range 21-410 days). The population was 28-85 years of age, 58% male, 42% female, 90% Caucasian, 6% Black, and 4% Asian and other. Table 4 lists adverse reactions reported in 10% or more of patients treated with DOXIL in combination with bortezomib for multiple myeloma.

**Table 4: Frequency of treatment emergent adverse reactions reported in ≥ 10% patients treated for multiple myeloma with DOXIL in combination with bortezomib, by Severity, Body System, and MedDRA Terminology.**

Adverse Reaction	DOXIL + bortezomib (n=318)			Bortezomib (n=318)		
	Any (%)	Grade 3	Grade 4	Any (%)	Grade 3	Grade 4
<b>Blood and lymphatic system disorders</b>						
Neutropenia	36	22	10	22	11	5
Thrombocytopenia	33	11	13	28	9	8
Anemia	25	7	2	21	8	2
<b>General disorders and administration site conditions</b>						
Fatigue	36	6	1	28	3	0
Pyrexia	31	1	0	22	1	0
Asthenia	22	6	0	18	4	0
<b>Gastrointestinal disorders</b>						
Nausea	48	3	0	40	1	0
Diarrhea	46	7	0	39	5	0
Vomiting	32	4	0	22	1	0
Constipation	31	1	0	31	1	0
Mucositis/Stomatitis	20	2	0	5	<1	0
Abdominal pain	11	1	0	8	1	0
<b>Infections and infestations</b>						
Herpes zoster	11	2	0	9	2	0
Herpes simplex	10	0	0	6	1	0
<b>Investigations</b>						
Weight decreased	12	0	0	4	0	0
<b>Metabolism and Nutritional disorders</b>						
Anorexia	19	2	0	14	<1	0
<b>Nervous system disorders</b>						
Peripheral Neuropathy*	42	7	<1	45	10	1
Neuralgia	17	3	0	20	4	1
Paresthesia/dysesthesia	13	<1	0	10	0	0
<b>Respiratory, thoracic and mediastinal disorders</b>						
Cough	18	0	0	12	0	0
<b>Skin and subcutaneous tissue disorders</b>						
Rash**	22	1	0	18	1	0
Hand-foot syndrome	19	6	0	<1	0	0

\*Peripheral neuropathy includes the following adverse reactions: peripheral sensory neuropathy, neuropathy peripheral, polyneuropathy, peripheral motor neuropathy, and neuropathy NOS.

\*\*Rash includes the following adverse reactions: rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, exfoliative rash, and rash generalized.

**Post Marketing Experience:** The following additional adverse reactions have been identified during post approval use of DOXIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Musculoskeletal and Connective Tissue Disorders:* rare cases of muscle spasms. *Respiratory, Thoracic and Mediastinal Disorders:* rare cases of pulmonary embolism (in some cases fatal). *Hematologic disorders:* Secondary acute myelogenous leukemia with and without fatal outcome has been reported in patients whose treatment included DOXIL. *Skin and subcutaneous tissue disorders:* rare cases of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

**DRUG INTERACTIONS:** No formal drug interaction studies have been conducted with DOXIL. DOXIL may interact with drugs known to interact with the conventional formulation of doxorubicin HCl.

**USE IN SPECIFIC POPULATIONS: Pregnancy:** Pregnancy Category D [see *Warnings and Precautions*]. DOXIL is embryotoxic at doses of 1 mg/kg/day in rats and is embryotoxic and abortifacient at 0.5 mg/kg/day in rabbits (both doses are about one-eighth the 50 mg/m<sup>2</sup> human dose on a mg/m<sup>2</sup> basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced live litter sizes.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs, including anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from DOXIL, discontinue nursing during treatment with DOXIL.

**Pediatric Use:** The safety and effectiveness of DOXIL in pediatric patients have not been established.

**Geriatric Use:** Of the patients treated with DOXIL in the randomized ovarian cancer study, 34.7% (n=83) were 65 years of age or older while 7.9% (n=19) were 75 years of age or older. Of the 318 patients treated with DOXIL in combination with bortezomib for multiple myeloma, 37% were 65 years of age or older and 8% were 75 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

**Hepatic Impairment:** The pharmacokinetics of DOXIL has not been adequately evaluated in patients with hepatic impairment. Doxorubicin is eliminated in large part by the liver. Thus, DOXIL dosage should be reduced in patients with impaired hepatic function [see *Full Prescribing Information*].

Prior to DOXIL administration, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase, and bilirubin [see *Full Prescribing Information*].

**OVERDOSAGE:** Acute overdosage with doxorubicin HCl causes increases in mucositis, leucopenia, and thrombocytopenia. Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization, antibiotics, platelet and granulocyte transfusions, and symptomatic treatment of mucositis.

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## COME HOME, the Oncology Medical Home

(continued from cover)

articles have been published on the expenses incurred in emergency departments (EDs) and on the costs and consequences of hospitalizations. Patients hate to be in the hospital, and physicians hate to see patients get antibiotic-resistant infections, infectious diarrheas, bedsores, and all the other complications that can occur when patients are hospitalized.

COME HOME is built on the idea that if we can intervene, early and aggressively, in the sequelae of having cancer and its treatments, we can prevent complications that require hospitalization and ED visits. Patients stay healthier, stay home, and we save money with better care.

Over the years, it became increasingly apparent to me that keeping patients out of the hospital whenever possible made their lives better and my life easier. So we instituted policies and procedures at New Mexico Cancer Center to manage the side effects of cancer and its treatment. After we had been working on these policies long enough to generate data, I learned that we had saved the payers literally millions of dollars.

Health plans, including Medicare, have attempted to direct patients to lower-cost sites of service. Pilot projects have included nurse hotlines or navigators or care coordinators. The Congressional Budget Office has looked at the Centers for Medicare & Medicaid Services (CMS) pilots and concluded that inadequate savings have been achieved. My theory is that these systems don't work because the person trying to coordinate care is not part of the practice that is managing the patient. When the phone nurse gets beyond her or his comfort zone, she or he sends the patient to the ED to avoid potential problems.

### Replicating Success

At New Mexico Cancer Center, a physician-owned multi-disciplinary center, we instituted an integrated triage system where the nurses follow a written protocol and schedule patients accordingly. This requires same-day scheduling, patient education, and a team-based approach. In short, we created an oncology medical home, long before we knew to call it that. Our data show significant savings to the payers, but more expense to the practice, as many necessary services are not reimbursed. When the Center for Medicare and Medicaid Innovation offered an opportunity to apply for a grant that would allow us to demonstrate and expand our processes, I set up a company called Innovative On-

cology Business Solutions, Inc (IOBS), to write the grant and manage the project. IOBS was awarded \$19.8 million.

The award will test whether this process can be replicated in other practices across the country and can produce similar savings. We must demonstrate that the care we provide is at least as good as what is currently standard care (I expect it will be better), and that the model can eventually be sustainable. I have selected 6

**My theory is that these systems don't work because the person trying to coordinate care is not part of the practice that is managing the patient.**

additional practices across the country to participate.

Triage Pathways are the heart of the program. This provides a scripted response to patients who call with problems and is designed to result in the patient getting care at the right site of service immediately. Order sets for given problems are combined with same-day visits scheduled by the triage nurses according to the acuity of each patient's problem.

For example, a caregiver brought an 86-year-old man with pancreatic cancer to our cancer center with hypotension, no fever, hypoxia, and incoherence. Within an hour, we had labs back, cultures drawn, a CT completed to rule out pulmonary emboli, and his first liter of fluid and first dose of antibiotics given. By the time the hospital had a bed available for him, he was alert, conversant, and had normal blood pressure. He turned out to have *E coli* sepsis. Had he gone to the ED, that process would have taken hours. Leaving an elderly man shoky for hours could result in kidney damage or cardiac damage, and usually requires an intensive care unit visit or a prolonged hospitalization. Our intervention resulted in the patient complaining the next morning about cold coffee, and a discharge a few days later.

This is clearly better health, better healthcare, and lower costs.

### Creating the Infrastructure

However, significant infrastructure is required for a clinic to be able to respond as we can. Practices were selected based on their ability to create that infrastructure, which in healthcare means caregivers. Because those salaries and services are not paid for by the usual fee schedule, the grant money must cover it.

Each practice is experienced in the use of an electronic health record (EHR). Acquiring data in a time frame rapid enough to change behaviors is key. Part of the money will be used to develop a software system to extract clinical data and pathway compliance from the EHRs and to combine that with Medicare claims data. The pathway compliance data will be on the lead physician's dashboard weekly, giving him or her the ability to work with the physicians of the practice and stay on pathway. Physicians respond to data, and showing that other doctors can do a better job for their patients provides a very strong incentive to change behavior.

Patients enrolled into the process will be newly diagnosed Medicare patients with 7 cancer types. A physician-led team, supported by grant funds, will carefully monitor and educate patients. Patients developing problems will be cared for immediately, avoiding expensive complications. This process meets the concept of a Medical Home, and we hope to achieve NCQA certification.

We recognize that cancer patients will sometimes require hospitalization. When patients do require hospitalization, the admitting oncologist will be able to determine when that patient is stable enough to have therapy completed in the office. Extended hours will allow daily visits until the patient's acute event has resolved. Just having the patient admitted directly to the oncologist, bypassing the ED and the hospitalists, will avoid significant expense. Transitions of care will be minimized. We will be monitoring for readmissions and hospital-acquired infections.

### Rising Drug Costs

Hospitalizations and ED visits are only part of the increasing costs to the healthcare system for oncology. Drug costs are increasing to approximately 10% of healthcare costs, and cancer drugs account for a significant proportion of that cost. CMS and payers alike react to the increased costs with dismay and look to the delivery system for assistance. United Health Group and

Aetna both have pilot projects designed to control drug costs. Some payers have considered moving chemotherapy to the pharmacy benefit instead of leaving it in the medical benefit, in the forlorn hope that pharmacy benefit managers can solve the problem. Another option Congress is considering is to decrease the payment from Average Sales price +6% to something lower in hopes that use of drugs will diminish. Payers are hoping that defining pathways (specific therapies for specific cancers) will curb costs, and if that doesn't work, they hope strict prior authorization processes will decrease use.

If CMS decreases payment for drugs by either of the proposed mechanisms, the pharmacy inventory costs incurred by independent oncology practices will become overwhelming, and practices will not be in the business of chemotherapy administration. Unfortunately for CMS, the need for the chemotherapy will not diminish. The patients will just be referred to hospital-based infusion centers, and the price will increase. Both Avalere and McKesson data show higher costs for chemotherapy in hospital-based systems. In my practice I calculated the true overhead costs of maintaining inventory control of chemotherapy, and it is significantly higher than the 6% CMS allots. My ability to continue providing infusion services for Medicare patients depends on my ability to cost shift to commercial payers, who are increasingly indisposed to allowing cost shifting from government programs to be factored into their reimbursement schedules.

Pathway development will have a limited effect on drug costs as well. In the practices of the Oncology Circle (a group of 30+ oncology practices that share data) the vast majority of physicians are following NCCN guidelines. Once the practices become adherent to the pathways, and the outliers are brought into compliance, all the available savings from pathways will have occurred. Similarly, utilization review and prior authorization will not decrease costs in a significant way in oncology. The American Medical Association has calculated the increased costs of participating in prior authorizations as about \$1742 per doctor per year. Yet my experience is that I have never been turned down by a prior authorization peer reviewer. If literature exists to support my choice of therapy off label, or if therapy is listed in the guidelines, insurers are very reluctant to incur the wrath of cancer patients by denying care.

The basic problem is that all of these strategies are nibbling around the edges

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Mark McClellan, MD, PhD, talks about how to better inform providers regarding regulations and quality measures that are part of new delivery care models (<http://bit.ly/Tc94kb>)



of drug costs. I cannot control the costs, I must pay the price the manufacturer requires, and I must use the drugs. The nation has not shown the political will to take on PhRMA and truly address the problem of drug costs. They would prefer to aim at the easier target of the practicing physicians. But eliminating the low-cost provider of the services—physician fee schedule practices—will not solve the problem.

The COME HOME project will require pathways to be followed for both the diagnostic and therapeutic parts of what we do. The computerized data extraction will measure the compliance with the pathways on a nearly real-time basis. This will allow us to be certain that

**The basic problem is that all of these strategies are nibbling around the edges of drug costs. I cannot control the costs, I must pay the price the manufacturer requires, and I must use the drugs. The nation has not shown the political will to take on PhRMA and truly address the problem of drug costs.**

the standard of care is met. We do expect some savings from pathway adherence, but obviously the drug costs will continue.

Personalized medicine includes molecular diagnostics. These genetic tests are expensive and the field is rapidly evolving. Getting the appropriate markers at the appropriate time will provide better care by avoiding the use of ineffective therapy and focusing on targeted therapy where it is available. Our diagnostic pathways will include these markers, and we will work with a group of experts in the field to make sure our pathways are appropriate. We will include these data in our clinical and economic outcome results.

### Conclusion

If the COME HOME hypothesis is correct, and community oncology practices do provide quality care at a lower cost, in a setting more convenient to patients, we will work to export this model to practices and payers. If we understand the costs that must be covered in the office to avoid costs elsewhere, the payment structure will have to change. Hopefully, at the end of the 3-year grant, we will know what is included in an oncology bundle and the cost. Then, we can truly be paid for value and achieve Dr Berwick's Triple Aim. **EBO**

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**Focusing on Clinical and Economic Outcomes—Not Guidelines**

(continued from cover)

**EBO:** Healthcare payers are attuned to limited budgets and the possibility of rationing down the road. One way they seek to slow the growth in costs of oncology agents is by changing the distribution model, and moving toward the use of specialty pharmacy providers. Do you see that as a positive complement to provider side efforts to modulate the cost of cancer care?

**Dr Pecora:** I don't know if that will avoid a discussion of rationing, but I really hope we can avoid that. I do believe that we need to do something different.

Efforts to improve compliance with clinical pathways are not all that helpful because that is a surrogate of quality and a surrogate of cost-effectiveness. On the contrary, I believe we should just go straight at it. We should insist on a certain progression-free survival and overall survival outcomes at a given cost, and let the providers decide how they're going to accomplish that.

**We'll also be creating service bundles: If we treat a person with a very specific condition, you will get this outcome and we will charge you one price for this. We assume the risk.**

**EBO:** It sounds like trying to commoditize the quality outcome in cancer care.

**Dr Pecora:** This is a pathway away from having a nation of cooks and toward promoting a nation of chefs. If we set our sights on buying a specific outcome, then we can approach it like buying other products, such as a car or a computer tablet—you know what the output is, and you want the best possible cost to achieve it. That's where we have to get to in cancer care.

Here's a concrete example: If you know you can cure 80% of people us-

ing a 5-drug combination, but you can also cure 80% of people using a 2-drug therapy, we have to create the economic incentives to encourage prescribers toward that option. One might be to have the cost of the additional drugs come out of the pocket of the prescriber—that's a bit simplistic, but it's a critical point. This is different from saying, "We'll pay you a bonus because you complied with this pathway." We're targeting the outcome, not the surrogate for quality care.

Therefore, we may instead say, "There are various ways you can achieve this outcome, but here is what we're expecting to pay for this outcome. And, if you deliver it at this cost or even lower, there's room for you to make a profit like any other business. The lower the cost for delivering this quality outcome, the more you make." Now the incentive is completely aligned because you've pegged the outcome as the target. If the outcome is the target, there shouldn't be a concern about lowering quality as you're reducing cost.

**EBO:** So then the clinical pathway is basically irrelevant as long as it works?

**Dr Pecora:** That's right. The clinician can use any pathway that works, but he or she must obtain the best outcome at (or below) the benchmarked cost.

Let's use breast cancer as an example. A clinician may want to prescribe a patient adriamycin and cyclophosphamide, but paclitaxel and cyclophosphamide cost the same amount of money, with identical outcomes. Should we spend time tracking prescribers on how they use one or the other (and did they give the doses on time), or do I just want to track the thing that counts the most—the patient's outcome? If the outcomes are in line with what they should be, and the provider's costs are not above what the cost should be, then that's great. However, if the outcomes are poorer or the cost of treatment is greater than it should be, then my providers will hear from me.

Why shouldn't we measure as the key outcome of what people are delivering—overall survival and progression-free survival—as long as it's tied to an appropriate cost?

**EBO:** Let's talk about Regional Cancer Care Associates (RCCA). How long has RCCA been in existence and what is your overall mission?

**Dr Pecora:** We came into existence January 1, 2012, and our mission is to provide the highest quality innovative cancer care, at the best possible cost.

**EBO:** It seems like RCCA's 70 providers are spread throughout the state. Are they integrated in any form?

**Dr Pecora:** Well, we're 1 company. We have 1 tax ID number; 1 provider number. We have the same health resources, pension, etc.

We are codeveloping standards of care that the group is committed to following. We've already created new image guidelines that we're now following, which significantly reduce the amount of imaging that was otherwise done routinely in practice. The excess imaging procedures are not medically necessary and, in fact, they may be potentially harmful and waste money.

We're now preparing bundled packages that we will offer to payers for specific services. We want to sell products into the marketplace, not services.

**EBO:** Is your information technology system integrated as well? Can you share these pathways and medical records among practitioners?

**Dr Pecora:** Not to that extent—yet. We're integrated in that we have 1 billing system. We're integrated in terms of pathways. We will soon be integrated in terms of following the outcomes of our patients through a cancer outcome tracking and analysis (COTA) system. We haven't linked all of our electronic medical records yet.

**EBO:** You recently signed a contract with Horizon Blue Cross Blue Shield. How has this changed the ballgame for RCCA?

**Dr Pecora:** To their credit, Horizon sees the value of working with an organization of our scale, to work collaboratively to provide a high-quality product across the entire state at the best possible cost to their subscribers.

We'll achieve this in part by reducing expensive sites of service, reducing unnecessary testing, and reducing redundancy of testing. We'll also be creating service bundles: If we treat a person with a very specific condition, you will get this outcome and we will charge you one price for this. We assume the risk.

**EBO:** Do you have a baseline or database of benchmark costs that you're targeting for the individual types of cancer treated by your providers?

**Dr Pecora:** No, not yet. Our contract with Horizon helps us get there. In other words, we're working toward offering bundles, and it will take some time to get there. We're putting the

outcome tracking and analysis system into practice now, so that we can track outcomes and costs to create the database that we need to create the bundled charges. We will be able to show Horizon transparently the outcomes obtained with 1 particular treatment, which match the national standards for best practice. We will show Horizon the best outcomes we can achieve, and we will charge them this bundled amount, understanding our cost.

**EBO:** Are you seeking to expand the number of providers in New Jersey?

**Dr Pecora:** Yes. By the end of the year, we'll be over 100.

**EBO:** Will RCCA seek to contract through this model with accountable care organizations (ACOs)? It sounds like a great fit.

**Dr Pecora:** Well, not just now. Today's ACOs are based primarily in primary care. However, I do think that there will be relationship opportunities between RCCA and ACOs.

**EBO:** Do you think the RCCA model is an early vision of the future of cancer care if we will be able to modulate cancer care?

**Dr Pecora:** I don't think we can modulate the cost of cancer care and avoid rationing without controlling how and where care is delivered at scale. You need to drive out inefficiencies and waste and incentivize people to think, "If I do it this way instead of the way I used to do it, not only does the patient get the best outcome, but I'm driving down cost and I'm driving margin to my bottom line."

Like any other business, that's the incentive I want to create. **EBO**

**Participant Affiliation:** From Regional Cancer Care Associates; John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ.

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**Companion Diagnostic Testing in Payer Decision Making**
*(continued from cover)*

ment, personalized medicine is emerging as a critical game changer. A more complete understanding of cancer biology and the new tools complementing the field of companion diagnostics (CDx) offer the pharmaceutical industry the ability to target subsets of patients for testing and treatments—unleashing the potential for greater safety and efficacy, accelerated regulatory approval, and the possibility for value-based reimbursement. Payers are intrigued, yet remain cautiously optimistic.

A strategic decision to build a CDx program is a complex one. For top-performing pharmaceutical and diagnostic companies incorporating CDx into strategy, preparing for success involves developing consistent criteria and protocols to ensure success within budget.

A focus on biomarkers may help drive clinical trial enrollment, overall treatment efficiency, and a better understanding of previously failed therapies, all of which will likely help to accelerate approvals of life-enhancing and cost-effective therapies. For example, Novartis' failed drug, lumiracoxib (Prexige), may be resubmitted to the US Food and Drug Administration (FDA) with a CDx. If approved, this would be the first time

**The lack of standards, or a road map, for evidence-based development, commercialization, payer coverage, and value-based reimbursement presents a unique challenge to diagnostic development efforts.**

a “failed” drug has been rescued by using a CDx.<sup>1-4</sup>

There is an increased awareness in the pharmaceutical industry that drugs must be more “personalized” to optimize their effect and cost savings. Payers are starting to support this movement. According to Ira M. Klein, MD,

MBA, FACP, chief of staff, Office of the Chief Medical Officer, Aetna, “Let’s not look at the mean survival for a new drug...let’s look at who got 12 months additional survival, and who got almost none. Then, let’s ask if we can define another companion diagnostic to treat the right people.”

There are only approximately 40 drugs in the United States associated with CDx. In the past 5 years, most of the major pharmaceutical companies, including Abbott, Pfizer, Novartis, Bristol-Myers Squibb, Boehringer Ingelheim, and AstraZeneca, have incorporated CDx into their product strategy, as exemplified by their cancer drug development pipeline where there are more than 500 compounds targeting over 140 genomic alterations in trials. Many, once successfully commercialized, could result in a rapid proliferation of CDx into the cancer clinic.

**Business Model Issues**

A trend toward codevelopment of drugs and CDx stands in stark contrast to siloed development. Linking a molecular test to drug response requires a clinical trial. Ideally, codevelopment programs are initiated early in trials, but tests are often an afterthought. This paradigm is changing as more codevelopment successes have become public, and the pressure continues to mount on pharmaceutical companies to replace brand name medications coming off patent protection.

Divergent business models make commercialization of CDx difficult. Ironically, many diagnostic tests have been rewarded with more favorable reimbursement as a laboratory-developed test (LDT) than those that have been successfully cleared by the FDA. Additionally, it is unclear to most diagnostic companies how they will be compensated for the costly effort required to complement the pharmaceutical industry’s efforts, leaving many companies leery about entering into such arrangements.

Submitting a diagnostic with a drug might increase the therapeutic’s chances of being approved, and perhaps drive accelerated timelines. There have been several legislative proposals, such as the MODERN Cures Act, which create additional incentives for such partnerships. As pressure mounts on traditional diagnostic testing reimbursement, some diagnostic companies are starting to leverage their expertise via co-development arrangements with the pharmaceutical industry, thus securing some value-based revenue that offsets revenue declines from the traditional clinical testing line of business.

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Moderated by **David R. Gandara, MD**, this panel discussion explores best practices and guidelines in non-small cell lung cancer molecular testing. The discussion includes expert perspectives from Corey J. Langer, MD, Mark A. Socinski, MD, Alan B. Sandler, MD, and Anne S. Tsao, MD (<http://bit.ly/VXOh2j>).


**Regulatory Challenges**

The lack of standards, or a road map, for evidence-based development, commercialization, payer coverage, and value-based reimbursement presents a unique challenge to diagnostic development efforts. When considering a CDx partnership, trial and error often prevails in working through the process with the FDA. In July 2011, the FDA issued a draft guidance document for discussion about this hurdle; however, to date it has not been finalized.

That’s not to say that the FDA hasn’t made progress. It is increasingly more common for the FDA to change a drug label to include pharmacogenetic information. Of the 40 or so drugs currently associated with diagnostic tests, the FDA requires a non-branded CDx to be used for only approximately 5. Some drugs have updated labels that include recommendations to use a test (eg, warfarin), whereas the majority only have updated information about the possible genetic link to side effects and optimal dose.

For example, the FDA changed the labeling of colon cancer drugs cetuximab (Erbix) and panitumumab (Vectibix) to be prescribed only to people with nonmutated forms of the KRAS gene. It’s unclear how useful updating labels with recommended or informational items will be. Although irinotecan labeling now includes FDA-recommended genotyping for mutations in the *UGT1a1* gene that cause increased susceptibility to severe diarrhea in patients with cancer, the label doesn’t require it.

Many industry insiders have said that stronger prescriptive labeling is needed to make sure tests, such as those to genotype for mutations in the *UGT1a1* gene, are actually used to optimize drug therapy. Additional regulatory guidance on CDx development is urgently needed for the promise of companion diagnostic/pharmaceutical development to be realized.

**Access and Adoption**

Of course, what eventually matters is whether doctors can access and utilize CDx tests in the clinic. And, even

though some CDx tests have been approved by the FDA, proving real-world efficacy and cost-effectiveness has been elusive. In addition, if only FDA-cleared tests were allowed to be run as a condition of drug coverage, patient access would likely be compromised because many laboratories would choose not to run the approved in vitro diagnostic test kit, instead opting to develop and perform an internally validated Clinical Laboratory Improvement Amendments (CLIA)-regulated LDT version.

Another important issue is the lack of education and understanding about personalized medicine among most physicians and other stakeholders. Uptake for required CDx has been fair; however, most doctors still don’t know enough about the testing to consistently utilize this emerging approach in routine clinical practice.

In a recent Medco nationwide survey of more than 400,000 physicians, 98% agreed that genetics is an important consideration for drug therapy, yet only 10% said they felt comfortable with their knowledge about such testing. This issue is critical in cancer, in which a significant shift in mind-set from cytotoxic agents toward targeted therapies is in forward motion. It is becoming extremely confusing for even the most up-to-date physicians to stay on top of the latest knowledge, and rapid advances in technology will allow us to assess cancer at a much deeper level than existed previously.

**Emerging Companion Technology in Cancer**

Cancer has long been categorized and treated by its anatomic site of origin (eg, lung, breast, colon, and skin). More recently, molecular testing has been added to detect specific, or “hot spot,” mutations to identify patients for new treatments that target such mutations (eg, *EML4/ALK* and crizotinib).

To date, CDx tests in cancer have largely been single-gene, “hot spot” mutation tests and not comprehensive multi-gene tests. However, as the field of personalized medicine expands, many oncologists and pathologists recognize

the need to further categorize and treat cancers by the underlying alterations in the DNA that drive tumor growth. This change to a pathway approach represents significant challenges to the prevailing view on how CDx tests should be developed, approved, and commercialized.

#### Next Generation Sequencing: A New Approach to Companion Diagnostics

Given the increase in molecularly driven medicine, demand is increasing for revolutionary technologies that deliver fast, inexpensive, and accurate genomic information. Since 2004, the National Human Genome Research

Over time, NGS-based approaches are likely to replace many existing molecular tests (eg, KRAS and BRAF) that are currently run as PCR-based tests. Some are already starting to be replaced by NGS-based methods, which can identify and quantify the “hot spots” plus a broader range of alterations (eg, base pair substitutions, insertions/deletions, copy number alterations, and gene rearrangements). NGS also provides an attractive solution to the practicing physician who cannot possibly stay up-to-date as the number of CDx tests increases and will look for a one-stop solution to test all cancer genes.

**In the face of rapidly evolving technology and absence of a clear road map for decision making, there is a payer dilemma: how to quickly evaluate, cover, and pay adequately for CDx tests that provide a clear benefit to patients and the insurer, while ruling out those tests that are of no benefit.**

Institute has awarded more than \$100 million for the development of next-generation sequencing (NGS) technologies, which resulted in the rapid growth of NGS platforms designed to sequence large amounts of DNA much more efficiently than with previously existing technologies. The important applications of the technology have triggered a rapid migration into the clinic. In cancer applications, NGS provides substantial advantages over single-gene “hot spot” tests and, using very small amounts of precious tissue, can result in detection of a broad array, and perhaps more sensitive and accurate assessment, of genomic alterations, which can have a significant impact on therapeutic and care management decisions.

Many companies and academic medical centers have started utilizing this technology in their CLIA laboratories to further characterize multiple disease states for patient management, including commercial companies such as Life Technologies, as well as prominent cancer centers such as MD Anderson, Memorial Sloan-Kettering Cancer Center, St. Jude’s Children’s Hospital, University of Michigan, and Dana Farber.

However, NGS-based tests are not all created equal. There will always be substantial variation in development, resources required to perform the test, decision-support resources, and clinical usefulness among NGS-based tests for different clinical applications. This is particularly important when considering somatic versus germ line testing, as there will be differences in the sensitivity and specificity of sequencing, and there will be varying levels of bioinformatics required to successfully translate enormous amounts of data into actionable information.

The clinical use of NGS-based CDx testing is expected to grow at a much faster rate than the overall molecular testing market. Powerful clinical applications are being shown regularly in top-tier journals (eg, *The New England Journal of Medicine* and *Nature*) and national medical conferences (eg, American Society of Clinical Oncology, American Association for Cancer Research, and San Antonio Breast Cancer), and expanding evidence will drive broader use of NGS-based tests as the standard of care and ultimately replace many of the molecular tests in use today. Operational and data production costs

will continue to decrease, making the technology more accessible, and value-based coding, coverage, and payment required to realize the full potential of this innovation will occur through effective collaboration across stakeholders.

#### Payer Decision Making: A Growing Dilemma

Because CDx tests may help improve efficacy and outcomes while reducing adverse events associated with certain treatments, they can possibly save payers the costs associated with ineffective or harmful drug therapies. This is the basis for discussions about value-based payment of CDx that clearly yield substantial downstream improvements in outcomes and cost-effectiveness.

Because targeted drugs are often considered to be very expensive, a growing number of payers now require CDx to be performed prior to approving distribution and payment for certain drugs. Some payers even require the performing laboratory to download CDx test results as an additional set of data to drive informed decision making and authorization.

Many payers are eager to support CDx tests that enable clear decision making with proven clinical utility. However, unlike medical devices and drugs, there is no clear or standardized method of preparing evidence of clinical utility, establishing coverage, or setting a reimbursement rate for a CDx test. Instead, coverage and reimbursement is set on a case-by-case basis whereby payers determine what is best for their beneficiaries in terms of improving their quality of life and treatment outcomes with opportunities to reduce medical costs.

In the face of rapidly evolving technology and absence of a clear road map for decision making, there is a payer dilemma: how to quickly evaluate, cover, and pay adequately for CDx tests that provide a clear benefit to patients and the insurer, while ruling out those tests that are of no benefit.

#### Payer Role in the Future of Companion Diagnostics

Companion diagnostics can enable significant improvements in safety, efficacy, outcomes, and cost-effectiveness associated with many existing and new therapies. Payers interested in providing access to CDx tests by covering and paying for them can be of great help by supporting the following:

- Standardization necessary to create a clear road map for evidence-based development, commercialization, payer coverage, and value-based re-

imbursement of CDx tests

- Willingness to support innovations, such as next-generation sequencing and other emerging CDx technologies
- Transformation of the CPT coding process to enable rapid assignment for new CDx tests. **EBO**

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