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THE AMERICAN JOURNAL OF MANAGED CARE®

#1 IN CITATIONS & IMPACT FACTOR

Volume 19
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Evidence-Based Oncology

Healthcare Reform

New Approaches to Medicaid Expansion: Hybrid Plans Offer Alternatives for Covering More People

Stanton R. Mehr and Mary K. Caffrey

The US Supreme Court's decision to uphold the Affordable Care Act but allow states to decide whether to expand Medicaid[1] has raised a question in many states: Where political leaders have been opposed or split on President Obama's healthcare reforms, is it smart or foolish to cover more people?

While Republicans oppose healthcare reform more often than Democrats, having a Republican in the state house has not always doomed Medicaid expansion. Arizona Governor Jan Brewer, who famously wagged her finger at Obama on an airport tarmac, nonetheless stared down legislators in her own party until they added 300,000 people to the rolls. For New Jersey's Chris Christie, having a Democratic leg-

Pennsylvania Governor Tom Corbett

(continued on page SP299)

Regulatory Update

In Historic Vote, FDA Backs Perjeta for Pre-surgical Breast Cancer Treatment

Action Could Be Precedent for Faster Approvals in Earlier Settings

Ben Leach

Richard Pazdur, MD

The US Food and Drug Administration (FDA) granted accelerated approval September 30 to pertuzumab (Perjeta) in combination with trastuzumab and docetaxel for patients with HER2-positive breast cancer in the neoadjuvant setting.

The vote was not a surprise, as it came after a 13-0 vote, with 1 abstention, on September 12 by the FDA's Oncologic Drugs Advisory Committee (ODAC) in support of the drug combination.

This pertuzumab regimen is the first neoadjuvant regimen formally approved by the FDA for any type of cancer. The September 12 ODAC meeting was the first in which the committee was asked to consider recommending an oncologic drug for approval on the basis of pathologic complete response (pCR) as the primary end point in the pivotal clinical trials. The committee was asked to consider the question

(continued on page SP306)

Status in the States

In Louisiana, Will Privatization Affect Efforts to Stop Cancer?

Mary K. Caffrey

Just 3 governors made the *Modern Healthcare* Top 100 list for 2013, and Louisiana's Bobby Jindal was among them.[1] Jindal was included among the most influential weeks before the start of open enrollment under the Affordable Care Act, which featured elements he refused to roll out in his state. Louisiana would not have its own exchange to sign up enrollees, nor would it expand Medicaid.

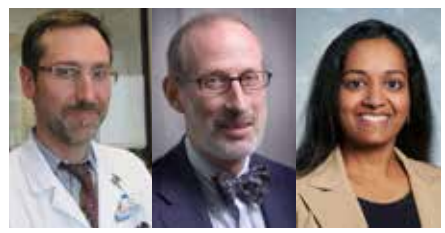
Louisiana Governor Bobby Jindal

That second decision has drawn loud and sustained criticism, given Louisiana's history of poverty, health disparities, and cancer, much of it linked to oil and chemical interests along the Mississippi River. The corridor between Baton Rouge and New Orleans has long been called "cancer alley," with many researchers noting the proximity of toxic emissions and cancer clusters among the poor.[2]

Jindal didn't just opt out of Obam-

(continued on page SP303)

Also in this issue...



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GRANIX™ is a new option in short-acting G-CSF therapy

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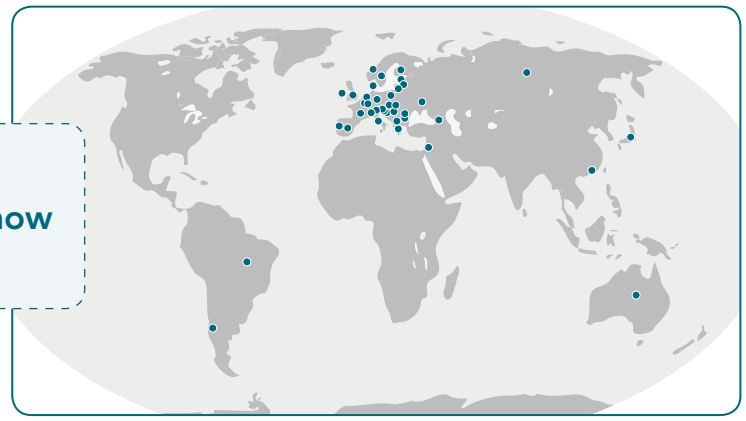
*As of August 2013.



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- Teva uses state-of-the-art manufacturing facilities and the most advanced testing equipment to produce quality biologics

‡Excluding supportive care.

Indication

- GRANIX is a leukocyte growth factor indicated for reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

Important Safety Information

- **Splenic rupture:** Splenic rupture, including fatal cases, can occur following the administration of human granulocyte colony-stimulating factors (hG-CSFs). Discontinue GRANIX and evaluate for an enlarged spleen or splenic rupture in patients who report upper abdominal or shoulder pain after receiving GRANIX.
- **Acute respiratory distress syndrome (ARDS):** ARDS can occur in patients receiving hG-CSFs. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.
- **Allergic reactions:** Serious allergic reactions, including anaphylaxis, can occur in patients receiving hG-CSFs. Reactions can occur on initial exposure. Permanently discontinue GRANIX in patients with serious allergic reactions. Do not administer GRANIX to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.
- **Use in patients with sickle cell disease:** Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disease receiving hG-CSFs. Consider the potential risks and benefits prior to the administration of GRANIX in patients with sickle cell disease. Discontinue GRANIX in patients undergoing a sickle cell crisis.
- **Potential for tumor growth stimulatory effects on malignant cells:** The granulocyte colony-stimulating factor (G-CSF) receptor, through which GRANIX acts, has been found on tumor cell lines. The possibility that GRANIX acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which GRANIX is not approved, cannot be excluded.
- **Most common treatment-emergent adverse reaction:** The most common treatment-emergent adverse reaction that occurred in patients treated with GRANIX at the recommended dose with an incidence of at least 1% or greater and two times more frequent than in the placebo group was bone pain.

Please see adjacent brief summary of full Prescribing Information.

References: 1. Data on file. Teva Pharmaceuticals: Filgrastim MA Approvals Worldwide. May 2013.
2. EvaluatePharma®, March 2013.

†Biologics License Application.

TEVA Oncology

GRANIX™
(TBO-FILGRASTIM)
Injection

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR
GRANIX™ (tbo-filgrastim) Injection, for subcutaneous use

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GRANIX is indicated to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

Splenic rupture, including fatal cases, can occur following administration of human granulocyte colony-stimulating factors. In patients who report upper abdominal or shoulder pain after receiving GRANIX, discontinue GRANIX and evaluate for an enlarged spleen or splenic rupture.

5.2 Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) can occur in patients receiving human granulocyte colony-stimulating factors. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.

5.3 Allergic Reactions

Serious allergic reactions including anaphylaxis can occur in patients receiving human granulocyte colony-stimulating factors. Reactions can occur on initial exposure. The administration of antihistamines, steroids, bronchodilators, and/or epinephrine may reduce the severity of the reactions. Permanently discontinue GRANIX in patients with serious allergic reactions. Do not administer GRANIX to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.

5.4 Use in Patients with Sickle Cell Disease

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disease receiving human granulocyte colony-stimulating factors. Consider the potential risks and benefits prior to the administration of human granulocyte colony-stimulating factors in patients with sickle cell disease. Discontinue GRANIX in patients undergoing a sickle cell crisis.

5.5 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte colony-stimulating factor (G-CSF) receptor through which GRANIX acts has been found on tumor cell lines. The possibility that GRANIX acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which GRANIX is not approved, cannot be excluded.

6 ADVERSE REACTIONS

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

- Splenic Rupture [*see Warnings and Precautions (5.1)*]
- Acute Respiratory Distress Syndrome [*see Warnings and Precautions (5.2)*]
- Serious Allergic Reactions [*see Warnings and Precautions (5.3)*]
- Use in Patients with Sickle Cell Disease [*see Warnings and Precautions (5.4)*]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [*see Warnings and Precautions (5.5)*]

The most common treatment-emergent adverse reaction that occurred at an incidence of at least 1% or greater in patients treated with GRANIX at the recommended dose and was numerically two times more frequent than in the placebo group was bone pain.

6.1 Clinical Trials Experience

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

GRANIX clinical trials safety data are based upon the results of three randomized clinical trials in patients receiving myeloablative chemotherapy for breast cancer (N=348), lung cancer (N=240) and non-Hodgkin's lymphoma (N=92). In the breast cancer study, 99% of patients were female, the median age was 50 years, and 86% of patients were Caucasian. In the lung cancer study, 80% of patients were male, the median age was 58 years, and 95% of patients were Caucasian. In the non-Hodgkin's lymphoma study, 52% of patients were male, the median age was 55 years, and 88% of patients were Caucasian. In all three studies a placebo (Cycle 1 of the breast cancer study only) or a non-US-approved filgrastim product were used as controls. Both GRANIX and the non-US-approved filgrastim product were administered at 5 mcg/kg subcutaneously once daily beginning one day after chemotherapy for at least five days and continued to a maximum of 14 days or until an ANC of ≥10,000 x 10^6/L after nadir was reached.

Bone pain was the most frequent treatment-emergent adverse reaction that occurred in at least 1% or greater in patients treated with GRANIX at the recommended dose and was numerically two times more frequent than in the placebo group. The overall incidence of bone pain in Cycle 1 of treatment was 3.4% (3.4% GRANIX, 1.4% placebo, 7.5% non-US-approved filgrastim product).

Leukocytosis

In clinical studies, leukocytosis (WBC counts > 100,000 x 10^6/L) was observed in less than 1% patients with non-myeloid malignancies receiving GRANIX. No complications attributable to leukocytosis were reported in clinical studies.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving GRANIX has not been adequately determined.

7 DRUG INTERACTIONS

No formal drug interaction studies between GRANIX and other drugs have been performed.

Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone-imaging results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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

In the embryofetal developmental study, pregnant rabbits were administered subcutaneous doses of tbo-filgrastim during the period of organogenesis at 1, 10 and 100 mcg/kg/day. Increased abortions were evident in rabbits treated with tbo-filgrastim at 100 mcg/kg/day. This dose was maternally toxic as demonstrated by reduced body weight. Other embryofetal findings at this dose level consisted of post-implantation loss, decrease in mean live litter size and fetal weight, and fetal malformations such as malformed hindlimbs and cleft palate. The dose of 100 mcg/kg/day corresponds to a systemic exposure ($AUC_{0\text{-}24}$) of approximately 50-90 times the exposures observed in patients treated with the clinical tbo-filgrastim dose of 5 mcg/kg/day.

8.3 Nursing Mothers

It is not known whether tbo-filgrastim is secreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GRANIX is administered to a nursing woman. Other recombinant G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates.

8.4 Pediatric Use

The safety and effectiveness of GRANIX in pediatric patients have not been established.

8.5 Geriatric Use

Among 677 cancer patients enrolled in clinical trials of GRANIX, a total of 111 patients were 65 years of age and older. No overall differences in safety or effectiveness were observed between patients age 65 and older and younger patients.

8.6 Renal Impairment

The safety and efficacy of GRANIX have not been studied in patients with moderate or severe renal impairment. No dose adjustment is recommended for patients with mild renal impairment.

8.7 Hepatic Impairment

The safety and efficacy of GRANIX have not been studied in patients with hepatic impairment.

10 OVERDOSAGE

No case of overdose has been reported.

TEVA Oncology

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Product of Israel

FIL-40046 July 2013

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

From the Publisher

THE AMERICAN JOURNAL OF MANAGED CARE®

The nation reached a turning point this month as exchanges let consumers enroll in health plans under the Affordable Care Act. Whether or not one thought this was a good thing, it has changed the delivery of healthcare as we know it. The customer has new clout, and everyone else must take notice. Early hiccups in the exchanges attributed to heavy traffic are a sign that people want to know what choices they have; whether most buy coverage remains to be seen. It will be months, perhaps years, before we know how healthcare reform will shape our delivery system. The only thing we know for certain is that change is coming.

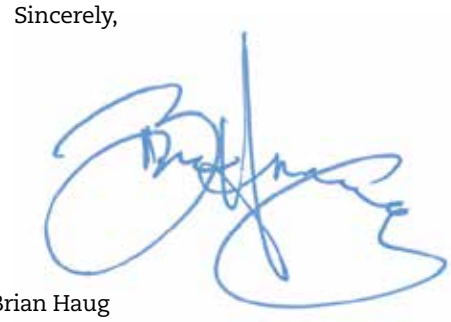
Reforms are seen every day on the front lines of research and clinical care. Almost every day we hear of a new approval or a fast-track or breakthrough designation for a cancer therapy, bringing hope to patients and families but also decisions for payers who must balance customer needs and cost concerns. This edition of *Evidence-Based Oncology* is full of news on the pharmaceutical front, including the US Food and Drug Administration's (FDA's) groundbreaking decision on Perjeta. Yet the need to weigh breakthroughs against the balance sheet is evident in our panel discussion on emerging issues in melanoma care, which took place just prior to the FDA's designation of priority review status for the combined use of Tafinlar and Mekinist. We hope you find the discussion as timely as we did.

The need to weigh breakthroughs against the balance sheet is evident in our panel discussion on emerging issues in melanoma care, which took place just prior to FDA's designation of priority review designation for Tafinlar and Mekinist. We hope you find the discussion timely.

We continue our Status in the States series with a look at Louisiana, where Governor Bobby Jindal has overhauled a charity hospital system that served 4 generations of Louisiana residents by creating public-private partnerships with leading healthcare providers. We spoke with top clinical officers of Ochsner Health Systems, a name synonymous with cancer care in New Orleans, to hear how that historic institution is adapting to Louisiana's changes while bringing the latest in cancer care delivery and research to its population.

Amid all the turmoil in our nation's capital, cancer care moves ahead. We thank you for reading and encourage you to follow updates on www.ajmc.com.

Sincerely,



Brian Haug
Publisher

EDITORIAL MISSION

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

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In This Issue...

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Expanding Medicaid
(continued from cover)

islature made Medicaid expansion easier. However, neither Arizona nor New Jersey set up a state-run exchange to enroll people in health plans.

But in other states, philosophical opposition to expanding a government program and concerns about long-term costs forced full-blown rejection of Medicaid Expansion or, in the case of places like Arkansas, Iowa, and Pennsylvania, attempts at hybrid plans. Waivers would allow states to craft their own versions of Medicaid, most with elements of privatization and one, in Pennsylvania, that would require, for the first time, that most new recipients look for work.

Table: Key Provisions of the Arkansas, Iowa, and Pennsylvania Waiver Applications

Plan Element	Arkansas	Iowa	Pennsylvania
Use of Private Health Plans for Newly Eligible?	Mandatory	Mandatory	Mandatory
Use of Premium Assistance	Yes	Yes	Yes
Plan Duration	2014-2016	2014-2018	2014–[a]
Estimated Newly Eligible Population	225,000	150,000	620,000
Enrollment in Private Plans	Yes	Yes	Yes
Proposed Coverage Groups	All newly eligible beneficiaries up to 138% of FPL	All newly eligible beneficiaries between 101% and 138% of FPL	All newly eligible beneficiaries up to 138% of FPL
Exempted Groups	Frail, dual eligibles	Frail, dual eligibles	Frail, dual eligibles
Premium Contributions	None	$20 per month	None
Copays	Same as existing state law for those at 100-138% of FPL; waived for others	Limited to nonemergency use of ED services (starting year 2)	Up to $25 per month[b]
Wraparound Benefits	Yes, paid by Medicaid	No	Yes
Other Features	Auto-assignment for beneficiaries who do not choose from at least 2 "Silver" level Marketplace plans	Financial penalties for low adherence to medical regimen and regular check-ups	Beneficiary work status to be reviewed to determine eligibility

ED indicates emergency department; FPL, Federal poverty level.
[a]Pennsylvania will evaluate the program within 2 years to determine if savings outpace its costs. If it is found to cost the state more, it will discontinue the program.
[b]Based on a sliding scale; premiums can be waived based on beneficiary participation in health improvement activities.
Sources: Musumeci M. Medicaid expansion through premium assistance: key issues for beneficiaries in Arkansas' section 1115 demonstration waiver proposal: issue brief. Kaiser Commission on Medicaid and the Uninsured. July 2013. http://kff.org/medicaid/issue-brief/medicaid-expansion-through-premium-assistance-key-issues-for-beneficiaries-in-arkansas-section-1115-demonstration-waiver-proposal/). Accessed September 20, 2013.
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Arkansas Opens the Door

On Friday, September 27, Arkansas Governor Mike Beebe received a phone call from US Health and Human Services Secretary Kathleen Sebelius that his state would be the first granted a waiver to pursue a so-called "private option," which will allow state residents to use Medicaid dollars to subsidize coverage obtained through private insurance. Up to 6 states may pursue some form of Arkansas' plan with 2, Iowa and Pennsylvania, filing waiver requests.

Beebe, a Democrat, said the waiver would allow about 218,000 Arkansans to receive private coverage. "Our actions have drawn positive attention from across the country, and now we will focus on getting this insurance to the Arkansans who need it to lead healthier, more productive lives," he said in a statement.[2]

The Arkansas, Iowa, and Pennsylvania plans all feature free-market aspects to the expansion of coverage—a unique "hybrid" strategy palatable to Republican or conservative Democratic legislators in their own states, and perhaps to conservative lawmakers elsewhere who have resisted expanding any government program.[3]

Indeed, at the recent Medicare-Medicaid conference sponsored by America's Health Insurance Plans, Daniel Crippen, executive director of the National Governors Association, said absent the willingness of the Centers for Medicare & Medicaid Services (CMS) to approve hybrid plans, he did not foresee additional Medicaid expansion until after the 2016 election cycle. "If there's more flexibility, the sooner the expansion will occur," he said.

Lack of expansion translates directly into lack of coverage. In June, researchers estimated that if 14 states opted out of Medicaid expansion, as allowed by the 2012 Supreme Court ruling, 3.6 million fewer people would be insured than if all of the states participated. These states would lose out on $8.4 billion in federal transfer payments. Furthermore, uncompensated care could cost these states another $1 billion by 2016.[4]

In most instances, the states' healthcare industries have been arguing loudly in favor of Medicaid expansion, based on the forecasts for greater revenues resulting from larger populations having coverage and seeking care. This has been putting state governments at odds with major local and regional businesses in largely Republican areas, an uncomfortable position for business-friendly elected officials.


Kathleen Sebelius

If Pennsylvania's waiver is approved by CMS, it would be the 26th state to expand Medicaid, and it could provide other hesitant state governors a usable pathway to not only cover more people and but also to accept federal assistance to take part in the program.

Evaluating the Hybrid Proposals

The common element of the hybrid plans is to use the health insurance exchange to increase coverage of the newly insured. Technically, this is not an expansion of Medicaid, though each state would use federal Medicaid dollars to provide subsidies to state residents who would, in turn, use the subsidies to purchase private insurance on the exchanges (now called the marketplace). This is also referred to as a "premium assistance" model.

This approach does not necessarily mean that low-income residents would obtain benefits equal to what they would have received in the traditional Medicaid program. This may be a key objection by critics and CMS alike. To address this gap, CMS would require the states to provide "wraparound coverage," which would ensure that members have the same level of benefit as any Medicaid beneficiary. This includes paying for any plan cost-sharing requirements above and beyond Medicaid's own out-of-pocket limits.[5] In addition, CMS will require that new beneficiaries have a choice of at least 2 qualified health plans in the marketplace before the agency will approve any section 1115 waiver request.

Arkansas' plan tightens its eligibility requirements for its state Medicaid program, leaving a greater share of the newly insured population to seek a plan on the exchange (income thresholds would be ratcheted down to a mere

(continued on page SP302)

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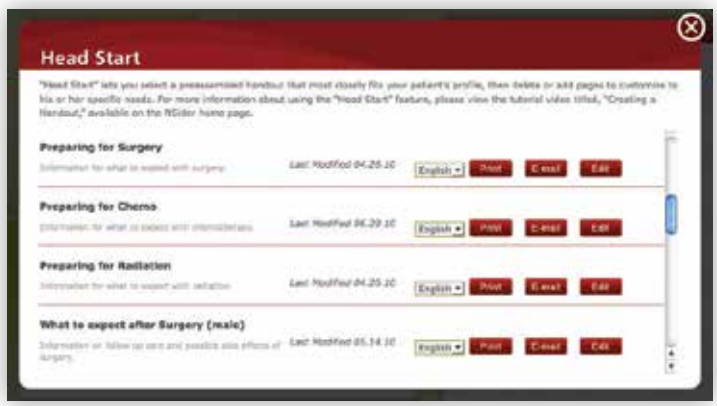

Head Start

Start with a preassembled handout and delete or add pages to customize to your patient's needs. Subjects include Basics on the patient's specific cancer type; Preparing for Surgery; Preparing for Chemotherapy; Preparing for Radiation; What to Expect After Surgery; What to Expect During Chemotherapy; What to Expect During Radiation; Support for Caregivers; and After Treatment. Specify gender, to further customize your handout.

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The NSider Patient Education Tool: Fast, Flexible, and Easy

Create practical, educational handouts, personalized to the needs of your patients living with cancer. The Tool was built by Eisai using the collective knowledge and expertise of nurses who have experienced cancer personally as survivors, caregivers, or simply as dedicated professionals with many years of service.

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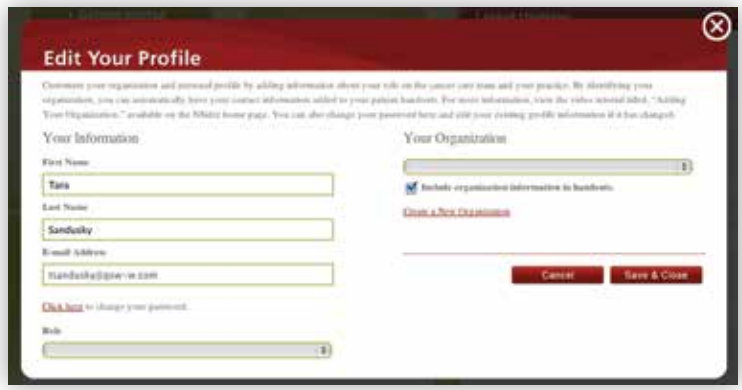

Edit Profile

Customize your organization's profile, as well as your personal profile, by adding information about your practice and your role on the cancer care team. You can automatically have your contact information added to your patient handouts by identifying your organization. You can also change your password here and edit your existing profile information if it has changed.

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Video Tutorials

The Quick Tour introductory video provides a short summary of the NSider Patient Education Tool home page, while demonstrating its various functions. Creating a Handout explains the three different ways to customize a handout for your patients. Sharing a Handout provides options for how to modify, use, and share a handout once you have created it. The Adding Your Organization video explains how to add contact information about your hospital, clinic, or organization.

Handout Wizard

Select from keyword criteria, enabling the NSider Tool to generate a custom handout. You can then add or delete pages as you wish to personalize it further.

Development of the NSider Website and the NSider patient education tool was funded by Eisai Inc., in consultation with a steering committee of experienced oncology nurses, compensated for their efforts. Nsider™ is a trademark and program of Eisai Inc.

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(continued from SP299)

Arkansas Governor Mike Beebe, center, signs legislation authorizating the private option for Medicaid expansion April 23, 2013. His state received federal authorization for the plan September 27, 2013.

17% of the federal poverty level, covering those with incomes up to 138% of that benchmark). Arkansas will require those entering the program to use the marketplace to choose a health plan for coverage. If this were voluntary, a section 1115 waiver would not be necessary.

Sandra Cook, consumer assistance specialist for the Arkansas Insurance Department, described the private option as a "win-win" while appearing at Diabetes Innovation 2013, a conference sponsored in Washington, DC, by the Joslin Diabetes Center of Harvard. "Insurers have guaranteed payment for 250,000 lives in Arkansas," she said, noting it will be at an insurance rate, not the Medicaid rate. This expansion of coverage into areas where the working poor live will encourage young doctors to locate in rural areas, she said, because they will be able to make a living. Private coverage, Cook said, doesn't carry the "stigma" that some feel when they are on public assistance programs.

Iowa Governor Terry Branstad

Pennsylvania seeks to address Medicaid expansion of the previously uninsured on many levels, including the use of premium assistance and private insurance plans, but notably, Governor Tom Corbett has added a provision onto the state's section 1115 waiver request: that coverage is contingent on a beneficiary's actively seeking a job. This may prove to be the most controversial part of Pennsylvania's application.

Sharon Ward, executive director of the Pennsylvania Budget and Policy Center, issued a white paper September 27 that stated "Federal law and policy prohibit premiums in the Medicaid program for anyone under 100% of the (federal poverty level) and the conditioning of health care coverage on job search and training requirements. The Corbett administration will be applying for a waiver to suspend those provisions of the law. Where CMS comes down on these issues remains to be seen."[6]

Additionally, Corbett is seeking to keep children in the state Children's Health Insurance Program, and out of the general Medicaid program, as directed by the ACA.[7] It is not known whether these provisions may be deal-breakers for CMS.

According to the Kaiser Family Foundation, CMS is willing to consider these section 1115 waivers as demonstration projects, and as such, may grant approval to a limited number of requests.[5] Whether this policy continues will determine how many states get the opportunity to pursue waivers.

Other Related State Action

On September 16, Michigan's Republican Governor Rick Snyder signed a law altering the state's Medicaid program that uses similar principles. In the Michigan law, newly insured beneficiaries can receive their health benefits through private insurance plans (not necessarily through marketplace plans, however).

John Z. Ayanian, MD, MPP, from the Institute for Healthcare Policy and Innovation, University of Michigan, wrote in the *New England Journal of Medicine,* "The key Democratic goal of expanding Medicaid coverage to low-income adults will be implemented in tandem with Republican objectives to control the state's healthcare costs, increase the role of private health plans, and require some new Medicaid enrollees to contribute toward the costs of their care."[8]

Crippen, of the NGA, said governors care about the quality of care, but they have no choice but to look for ways to control costs. "Until recently, states' top spending item was education," he said. "Healthcare, and Medicaid in particular, has crossed that line and is now the most expensive program in the states.

"Governors are looking very hard at the patients that cost the most, why they cost the most, and how we can change those practice or patterns to reduce their costs," Crippen said. Demonstration projects in states are just now bearing fruit, and governors will implement what they learn over the next few years, he said.

New Hampshire is another state with a Republican-controlled legislature but with a Democratic governor. Local news organizations have reported that the Republican-controlled state senate has formed a commission to determine if Arkansas' premium assistance–based hybrid plan would work for the state.[2] New Hampshire Governor Maggie Hassan is seeking quick action, wanting to begin Medicaid expansion by the beginning of 2014 to take advantage of those enticing federal dollars. **EBO**

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Louisiana
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acare. He crusaded against it, writing op-eds in national publications. As an alternative, he designed a path of privatization to deliver care to the poor, one that retains some elements of Louisiana's famous two-tiered hospital system while shedding others. Before Jindal's trusted health and hospitals secretary, Bruce Greenstein, resigned following a scandal, the two brought privatization and managed care elements to Medicaid as well.[3]

While privatization has both fans and critics—it has already resulted in the Louisiana State University hospital system laying off more than 1500 employees[4]—the bigger tumult came over Jindal's denial of Medicaid to at least 214,000 Louisianans who might be eligible under the ACA.[5] What outrages critics is Jindal's perceived departure from his original plan, "Louisiana Health First," unveiled in November 2008.[6]

For decades, critics of Louisiana's charity hospital system asked whether the poor were best served with a system of healthcare segregation. The new arrangement does not fully dismantle the divide.

That blueprint, which came as Louisiana crawled back from Hurricane Katrina, called for expanding Medicaid to more caretakers of eligible children, or at least more additional low-income persons with chronic conditions.[6] Offering the poor healthcare choices and providing preventive care at medical homes were seen not as dreams but possibilities, given Jindal's expertise as a state and federal health official.

As Jindal built a modern academic medical center to replace New Orleans' battered Charity Hospital, it seemed he would build a healthcare delivery system to match. The announcement came as 4 institutions—Ochsner Health System, and Tulane, Xavier and LSU—began to show the fruits of investing tobacco tax dollars on the Louisiana Cancer Research Consortium (LCRC).[7]

Among its goals, the consortium seeks better screening and earlier diagnosis, to combat a phenomenon common among the poor: cancer mortality is worse than cancer incidence, because too often patients are not seen until their disease has progressed beyond a point where it can be treated effectively.

According to LCRC:

- In 2011, approximately 22,780 new cancer cases were diagnosed in Louisiana, excluding some skin cancers and carcinomas.
- About 8360 people living in Louisiana died from cancer during 2011.
- Although cancer mortality is improving, rates in Louisiana remain about 30% higher than the rest of the country.[7]

Beyond the political and media uproar, some amazing things are happening in cancer care in Louisiana. The growth of the New Orleans–based Ochsner Health System, its relationships with the state's medical schools, and its decision to take over struggling institutions has allowed personalized medicine and cancer treatment pathways to take hold in places where change can come slowly.

Ochsner, LSU, and Tulane collaborate through LCRC, and Ochsner is moving beyond treatment trials to preventive ones for breast and prostate cancer, 2 diseases that hit harder than normal here. So what's the concern? While Jindal's approach to upending Louisiana's one-of-a-kind charity care system could spur even more collaboration, the failure to expand Medicaid means not everyone with cancer will get the same access, at least not now.

Toward a Public-Private Partnership

Over the past year, the big healthcare story in Louisiana has not involved cancer or the Affordable Care Act. It's been about the transformation of Louisiana's unique charity hospital system, which dates to 1736 and flourished under the populist governor Huey P. Long. Under Jindal, 9 of the state's 10 charity institutions will convert from LSU management into public-private partnerships.

Five such partnerships are in place, with the remaining 4 set to begin in 2014. Proponents, led by Jindal, say the new system will reduce costs, improve care for patients, and offer better training for medical students. In an editorial published in July, Jindal claimed the partnerships were "on target" to save $125 million this year.[8] Certainly, there is much in Louisiana's old system to be desired; an Institute of Medicine study released in August found 6 of the 10 highest cost cities for Medicare were in Louisiana.[9] (Among the cost drivers was a need to shed retirement obligations for the thousands of public employees in the hospital system; Jindal stated that the changes would wring out $82 million in annual savings.)[8]

For decades, critics of Louisiana's charity hospital system asked whether the poor were best served with a system of healthcare segregation. The new arrangement does not fully dismantle the divide; the poor are still in separate facilities, but through partnerships these hospitals are now buttressed with private funding, management, and clinical expertise. Some critics predict private partners are biding their time and will absorb losses from the safety-net hospitals until Jindal leaves office, when Louisiana will expand Medicaid.

The partnerships are quite complex. Louisiana retains ownership of safety-net hospital buildings, while the private partnership manages them and pay the state lease payments. In return, the private partners receive a share of

Historic Charity Hospital, known for decades by local residents as "Big Charity," now stands shuttered on Tulane Avenue in downtown New Orleans. Despite a top-to-bottom scrubbing by the military after Hurricane Katrina, it never reopened. Louisiana is now building a new hospital complex in a different part of the city that will operate under a public-private partnership. Some question how the new hospital will succeed financially without Medicaid expansion.

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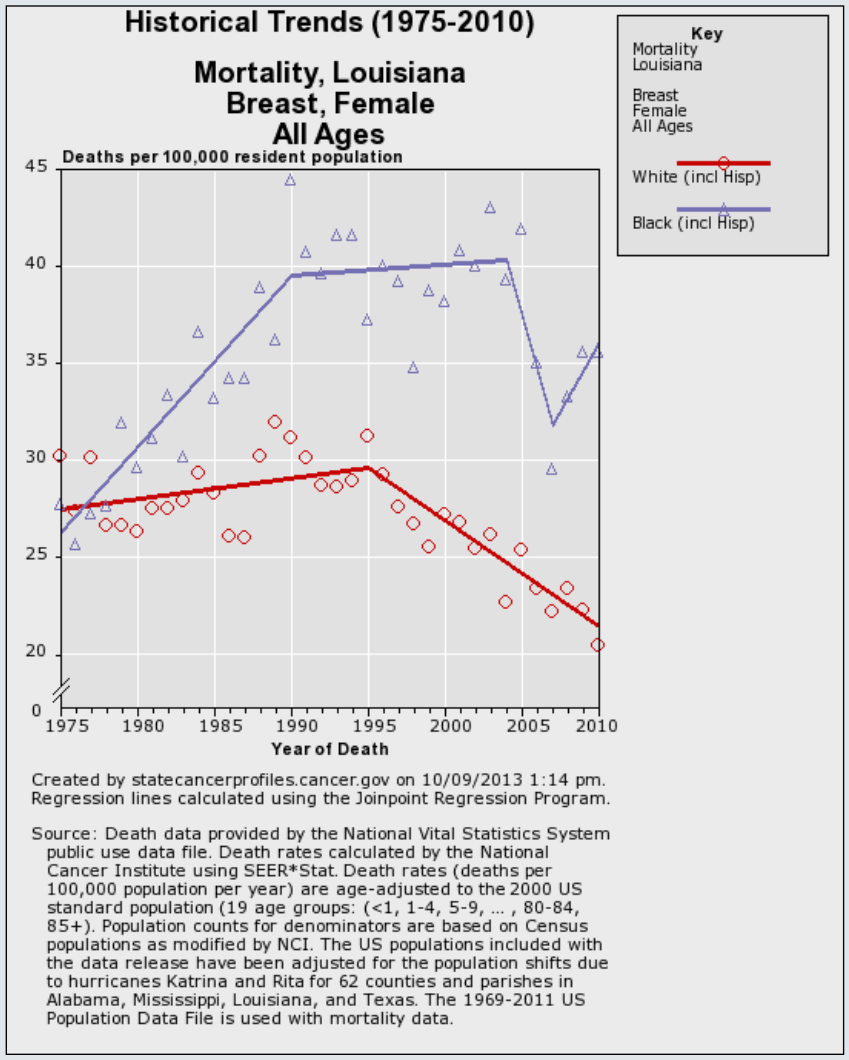
Figure 1. Screening Slows Breast Cancer Deaths



Louisiana's advent of breast cancer screening for underserved populations in 2002 led to an immediate decline in the mortality rate among African American women. Population dislocations after hurricanes Katrina and Rita reversed that progress temporarily, but experts say that screening is important long term to reducing cancer mortality.

Medicaid funds, starting with a guaranteed amount.

An interview with 2 top Ochsner physicians revealed the pluses and minuses of Jindal's approach: Ochsner's partnership with Leonard J. Chabert Hospital in Houma, Louisiana, gives that safety-net hospital access to management and medical expertise it might otherwise lack. According to Ochsner Executive Vice President and Chief Medical Officer Joseph E. Bisordi, MD, FACP, Chabert is run just like any other hospital in Ochsner's system.

Thus, the partnerships can provide a different level of "access" for cancer patients who have coverage through Medicare or Medicaid. But therein lies the issue. For patients with incomes between Medicaid eligibility levels and 133% of the federal poverty line, "I am not sure we have an answer for those folks," said John Cole, MD, who is Ochsner's chair for hematology and oncology.

Steve Spires, health policy analyst for the Louisiana Budget Project, a nonpartisan research organization, said that the failure to expand Medicaid has long-term implications for the public-private partnerships, because state taxpayers will continue to experience the fallout of sick people overwhelming hospitals instead of seeking preventative care or catching cancer when it is treatable.

"The taxpayers will end up paying for this care," Spires said. With cancer in particular, he said, "They will end up paying more than if we had paid for the preventive screening up front."

Saving Lives Through Early Detection

The refusal to expand Medicaid frustrates those who have seen positive developments in healthcare over the past decade, including efforts to expand coverage for uninsured children and increase cancer screenings. A decade ago things seemed on the upswing, when Louisiana's Legislature approved a tobacco tax to create the LCRC and seek a National Cancer Institute (NCI) designation within the state by promoting clinical trials.

Donna Williams, MPH, DrPH, has had a front-row seat for the decline in breast cancer mortality over the past decade. As director of Louisiana Cancer Control Programs for the LSU School of Public Health, she knows that early detection saves lives, because she has the data to prove it.

In 1995, the breast cancer screening rate in Louisiana for African American women was 59.1%, compared with a national average of 70.2%, putting Louisiana 48th among the states. LSU's screening program launched in 2002, and data from the Centers for Disease Control and Prevention (CDC) revealed an immediate, steep drop in mortality among African American women, which later reversed somewhat after the massive population shifts following Hurricane Katrina.[10,11]

By 2010, Williams said, Louisiana ranked 22nd among the states for 2-year mammography screening, with a rate of 76.3%, slightly higher than the national average of 75.2%. Louisiana screened 78.3% of African American women in 2010, compared with a national rate of 78.9%.[10] Breast cancer mortality rates for all women remain well below 2002 levels, according to CDC data. **(Figure 1.)**[11]

But the good news with breast and cervical cancer is not repeated in other cancers, Williams said. Many who spoke with *Evidence-Based Oncology* decried Louisiana's low eligibility levels for Medicaid, which typically leave the uninsured with long waits for care once cancer is diagnosed, assuming it is diagnosed in time.

> *"People die as a consequence of this. That is not an exaggeration. You can say people have access to oncology lists, but if the waiting list is so long and people die waiting, what kind of access do people really have?"*
>
> **—Moriba Karamoko,**
> Louisiana Consumer Healthcare Coalition

As Williams and others explained, federal law requires Medicaid coverage once breast or cervical cancer is diagnosed. "They have fast-track qualification," Williams said. "It's a 2-pager; the providers attach the medical documentation and it goes through in less than 2 weeks."

By contrast, "If you have prostate cancer, you're out of luck," she said. "We don't have any programs specific to the other cancers." Much will depend on where a patient lives; those who use New Orleans' current replacement for the defunct Charity Hospital fare comparatively well to those in remote areas, Williams said. Those familiar with the experiences of Louisiana's uninsured say long waits and travel times can be as deadly as the cancer itself.

"People die as a consequence of this. That is not an exaggeration," said Moriba Karamoko, director of the Louisiana Consumer Healthcare Coalition. "You can say people have access to oncology lists, but if the waiting list is so long and people die waiting, what kind of access do people really have?"

A Complex History With Cancer

The Louisiana lifestyle, one that appreciates drinking, smoking, relaxing, and enjoying rich food (often fried), seems almost tailor-made to promote the kinds of cancers that are common in the state: lung, prostate, colorectal. Overlay an impoverished population, with demographics that tilt toward obesity, diabetes, and other risk factors associated with cancer, and it's not a surprise that the state's numbers are so high.

But another factor has been at work for decades: Louisiana's relationship with industry. Because there are so many demographic and lifestyle factors in play, it has been impossible to prove that oil, gas, and chemical interests are responsible for even higher cancer incidence rates in certain areas of the state. The proximity of industry to cancer clusters in certain zip codes along the Mississippi, as well as western parishes like Cameron and Calcasieu, has long been noted.[2] **(Figure 2.)**

Wilma Subra, a Louisiana native and winner of a MacArthur "genius" grant, gave up a career as a chemist for Gulf South Research 30 years ago. She founded a company to gather the science in support of residents who believed toxins from the plants near their homes were making them sick.

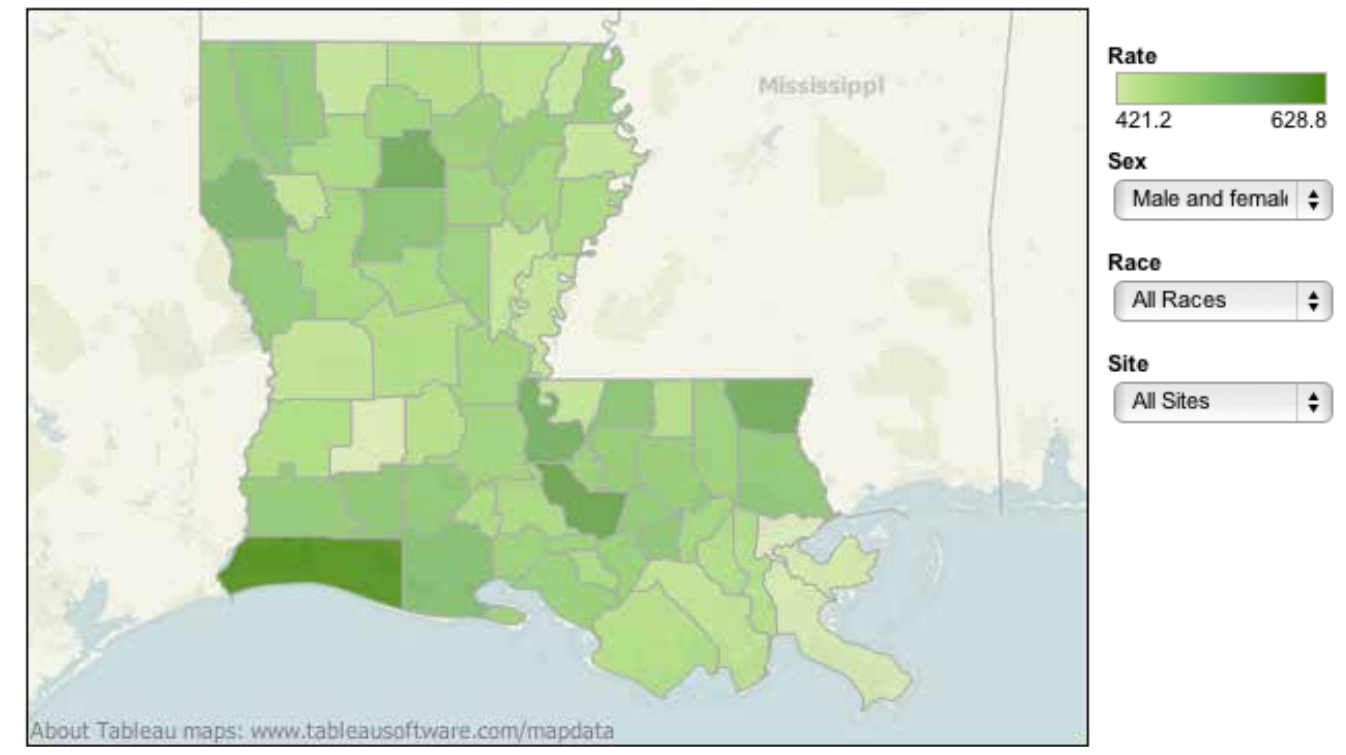
She was able to document how the

burning of toxic waste as fuel contributed to a spike in neuroblastomas in Amelia, Louisiana, and a judge ordered the facility closed.[12] Subra told *EBO* that she has seen elevated levels of lung, brain, and organ cancers in areas where concentrations of polyvinyl chloride "are way over acceptable standards." For years, she has worked with residents of Mossville, Louisiana, a community of mostly African Americans surrounded by chemical plants.

Subra says she's no expert on healthcare policy, but the people she works with need more than they are getting. "We have a desperate need for medical care due to the toxic exposure," she said. Young doctors rotate in and out, and they don't always understand what they are seeing. She would like to see toxicologists on hand permanently; specialists are needed to treat the complex conditions that patients experience. But that requires money; either direct funding, or residents with Medicaid or health insurance.

"The community thinks there should be a free clinic," Subra said. "But when you say 'free' industry goes beserk."

Figure 2. Louisiana Cancer Incidence Rates 2005-2009 Combined by Race, Sex, Site, and Parish



Source: Louisiana Tumor Registry. According to SEER data from the National Cancer Institute, cancer mortality rates for both white and black Louisiana residents are higher than US averages.

Ochsner's Growth, Into the Community

For decades, if you lived in Louisiana, or on the Gulf Coast of Mississippi or Alabama, and your doctor said, "Cancer," the next word was, "Ochsner." The renowned clinic was founded by Alton Ochsner MD, who was among the first to document the link between cancer and cigarette smoking; despite being criticized for this pronouncement, he opened the first group medical practice in New Orleans in 1942.[13]

By fate of geography, Ochsner did not flood in 2005 during Hurricane Katrina and was able to stay open to serve residents after other hospitals went dark. Already a growing presence in Louisiana, it bought 3 hospitals in 2006,[14] cementing a strong "system" that Bisordi said will be key to delivery cancer care going forward. "One of the advantages we have as a system that you may not have as a small community hospital, you don't have the structure to be more efficient. We have the resources in our system," he said.

In addition, Ochsner enjoys good collaborative relationships with LSU and Tulane medical schools, which have programs to boost minority participation in clinical trials, Bisordi said. "Some of the patient samples from clinics at Ochsner go for analysis at LSU," he said.

Today, Bisordi and Cole say their goal is to keep patients as close to home as possible for cancer care. Ochsner does more clinical trials by far than any other cancer center in Louisiana—Bisordi said about 6% of the 2600 new cancer patients who come through its system participate in one. Yet not all come to the main hospital on Jefferson Highway, right outside New Orleans. "Our thinking with the community hospitals is, 'We don't want the folks you can take care of.' Cole said, "care is best delivered closest to home."

Cole said the Ochsner system is developing consistent, evidence-based pathways for cancer care delivery, which will be shared at the community level with all hospitals and clinics. This is the expressed goal of the Affordable Care Act—to promote cost savings by developing measurable methods to provide care, not by withholding it.

If cancer care delivery improves, but a group of Louisianans lacks the means to receive it, what happens?

The Rev. Fred Kammer SJ, a Jesuit priest, Yale-educated lawyer and the former head of Catholic Charities USA now based at Loyola University New Orleans, has written about Medicaid expansion. He said that the discussion of the issue remains elevated among opinion leaders in the state. "It's a scandal," he said.

As the exchanges opened, Spires, of the Louisiana Budget Project, agreed. "Once people see the inequity, that people below the 133% of the poverty line get nothing, it's going to turn up the heat. It's by no means an issue that's going to go away."

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Perjeta

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of whether pertuzumab demonstrated "a favorable benefit-to-risk evaluation for the neoadjuvant treatment of early breast cancer."

"It's not every day that this committee gets to consider a new indication in breast cancer," said ODAC chair Mikkael Sekeres, MD, MS, associate professor of cedicine in the Department of Hematologic Oncology and Blood Disorders at the Cleveland Clinic Taussig Cancer Institute in Ohio.

The ODAC and subsequent FDA votes could be precedent-setting and result in much earlier approvals for drugs in earlier disease settings. "Early disease is the setting where we can have the biggest impact on long-term survival," Jose Baselga, MD, PhD, physician-in-chief at Memorial Sloan-Kettering Cancer Center in New York, told the ODAC panel.

Baselga served as primary investigator of the CLEOPATRA trial, which resulted in the FDA's approval of this same pertuzumab regimen in the metastatic setting, and he is also a primary investigator in the APHINITY trial, which is evaluating the efficacy of this pertuzumab regimen in the adjuvant setting. He said that, typically, the time between a drug's approval in the metastatic setting and its subsequent approval in an earlier setting is "simply much too long."

He gave the examples of docetaxel and trastuzumab, where 8 years passed between the approvals of each drug in the metastatic and adjuvant settings, respectively. In the case of pertuzumab, Baselga said that its efficacy has been well established in clinical trials and will continue to be assessed in the APHINITY trial in the adjuvant setting, with results expected to become available in late 2016.

However, Baselga indicated that an approval of pertuzumab in the neoadjuvant setting now, a full 3 years prior to when those results will become available, could have an immediate impact on patients.

"In terms of survival, even though trastuzumab has had a profound impact, a substantial number of patients are still dying from HER2-positive disease," Baselga said. "I feel strongly that we should make this therapy available to [patients] now."

Whether to Set a Precedent

Much of the discussion among ODAC members concerned the potential precedents set by approving an oncologic drug in the neoadjuvant setting.

The pivotal trials at the center of this supplemental biologics license application were relatively small compared with many of the clinical trials that have resulted in the approval of drugs for breast cancer in the metastatic setting, enrolling on the order of a couple of hundred patients as opposed to multiple thousands of patients. Therefore, these trials were not powered to determine survival information.

Despite several meta-analyses showing an association between pCR and survival benefits, no definitive answer has been derived from these studies as of yet.

"We shouldn't be assuming what the survival will be when the study is not powered to show that," said Antonio Tito Fojo, MD, PhD, program direc-

tor of medical oncology at the National Cancer Institute and one of the members of ODAC. Fojo abstained from the September 12 vote.

Among the concerns raised by other members of ODAC were the fact that the benefit may be more pronounced in hormone receptor-negative patients; whether docetaxel will be the chemotherapy that oncologists prefer to use with pertuzumab and trastuzumab should the regimen receive approval; and what long-term toxicities might be demonstrated when more data become available.

However, in addition to the way the regimen may affect individual patients, Richard Pazdur, MD, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research, asked ODAC to consider the potential benefits to society as a whole if the drug, once approved, did indeed reduce the disease

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burden in patients with early stage, HER2-positive breast cancer.

The results of 2 trials were at the center of much of the discussion: the NEOSPHERE trial and the supportive TRYPHAENA trial.

In the NEOSPHERE trial, a multicenter, open-label, phase II study, treatment-naïve patients with HER2-positive breast cancer were randomly assigned in a 1:1:1:1 ratio and stratified by operable, locally advanced, and inflammatory breast cancer as well as hormone receptor expression.[1] These patients received 4 neoadjuvant cycles of either trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) plus docetaxel (75 mg/m^2, escalating, if tolerated, to 100 mg/m^2 every 3 weeks; n = 107; group A); pertuzumab (loading dose 840 mg, followed by 420 mg every 3 weeks) in combination with the group A trastuzumab and docetaxel regimen (n = 107; group B); the pertuzumab and trastuzumab regimens without docetaxel (n = 107; group C); and pertuzumab plus docetaxel (n = 96; group D). The primary end point of the

study was pathological complete response (pCR).

Patients who received the combination of pertuzumab, trastuzumab, and docetaxel had a pCR rate of 45.8% (95% confidential interval [CI], 36.1-55.7), a significant improvement over patients who received trastuzumab and docetaxel without pertuzumab, who had a pCR rate of 29% (95% CI, 20.6 -38.5; P = .014). The pCR rates for the remaining 2 groups were 24% in those who received pertuzumab and docetaxel without trastuzumab (95% CI, 15.8-33.7), and 16.8% in patients who received pertuzumab and trastuzumab (95% CI, 10.3-25.3).The most common grade 3 or higher side effects observed in the 4 groups were neutropenia (61, 48, 1, and 52 patients in the 4 groups, respectively), febrile neutropenia (8, 9, 0, and 7, respectively), and leukopenia (13, 5, 0, and 7, respectively). The number of adverse events was similar in the 3 groups (A, B, and D) that received chemotherapy as part of their treatment regimen, with 15 to 20 serious adverse events per group in 10% to

Check serum lipase every 2 weeks for the first 2 months and then monthly thereafter or as clinically indicated. Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol abuse. Dose interruption or reduction may be required. In cases where lipase elevations are accompanied by abdominal symptoms, interrupt treatment with Iclusig and evaluate patients for pancreatitis *[see Dosage and Administration (2.3)]*. Do not consider restarting Iclusig until patients have complete resolution of symptoms and lipase levels are less than 1.5 x ULN.

5.6 Hemorrhage

Serious bleeding events, occurred in 5% (22/449) of patients treated with Iclusig, including fatalities. Hemorrhagic events occurred in 24% of patients. The incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Cerebral hemorrhage and gastrointestinal hemorrhage were the most commonly reported serious bleeding events. Most hemorrhagic events occurred in patients with grade 4 thrombocytopenia *[see Warnings and Precautions (5.9)]*. Interrupt Iclusig for serious or severe hemorrhage *[see Dosage and Administration (2.3)]*.

5.7 Fluid Retention

Fluid retention events judged as serious occurred in 3% (13/449) of patients treated with Iclusig. One instance of brain edema was fatal. Serious fluid retention events in more than 1 patient included: pericardial effusion (6/449, 1%), pleural effusion (5/449, 1%), and ascites (2/449, <1%).

In total, fluid retention occurred in 23% of the patients. The most common fluid retention events were peripheral edema (16%), pleural effusion (7%), and pericardial effusion (3%).

Monitor patients for fluid retention and manage patients as clinically indicated. Interrupt, reduce, or discontinue Iclusig as clinically indicated *[see Dosage and Administration (2.3)]*.

5.8 Cardiac Arrhythmias

Symptomatic bradyarrhythmias that led to a requirement for pacemaker implantation occurred in 3 (1%) Iclusig-treated patients. The cardiac rhythms (1 case each) identified were complete heart block, sick sinus syndrome, and atrial fibrillation with bradycardia and pauses. Advise patients to report signs and symptoms suggestive of slow heart rate (fainting, dizziness, or chest pain).

Supraventricular tachyarrhythmias occurred in 25 (5%) Iclusig-treated patients. Atrial fibrillation was the most common supraventricular tachyarrhythmia and occurred in 20 patients. The other supraventricular tachyarrhythmias were atrial flutter (4 patients), supraventricular tachycardia (4 patients), and atrial tachycardia (1 patient). For 13 patients, the event led to hospitalization. Advise patients to report signs and symptoms of rapid heart rate (palpitations, dizziness).

5.9 Myelosuppression

Severe (grade 3 or 4) myelosuppression occurred in 48% (215/449) of patients treated with Iclusig. The incidence of these events was greater in patients with accelerated phase CML (AP-CML), blast phase CML (BP-CML) and Ph+ ALL than in patients with chronic phase CML (CP-CML). Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated, and adjust the dose as recommended *[see Dosage and Administration (2.2)]*.

5.10 Tumor Lysis Syndrome

Two patients (<1%) treated with Iclusig developed serious tumor lysis syndrome. Both cases occurred in patients with advanced CML. Hyperuricemia occurred in 7% (30/449) of patients, the majority had chronic phase CML (19 patients). Due to the potential for tumor lysis syndrome in patients with advanced disease (AP-CML, BP-CML, or Ph+ ALL), ensure adequate hydration and treat high uric acid levels prior to initiating therapy with Iclusig.

5.11 Compromised Wound Healing and Gastrointestinal Perforation

No formal studies of the effect of Iclusig on wound healing have been conducted. Based on the mechanism of action *[see Clinical Pharmacology (12.1)]*, Iclusig could compromise wound healing. Serious gastrointestinal perforation (fistula) occurred in one patient 38 days post-cholecystectomy.

Interrupt Iclusig for at least 1 week prior to major surgery. The decision when to resume Iclusig after surgery should be based on clinical judgment of adequate wound healing.

5.12 Embryo-Fetal Toxicity

Iclusig can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. Ponatinib caused embryo-fetal toxicity in rats at exposures lower than human exposures at the recommended human dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Advise women to avoid pregnancy while taking Iclusig *[see Use in Specific Populations (8.1)]*.

6 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 with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The following adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Thrombosis and Thromboembolism *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2) and Dosage and Administration (2.3)]*
- Congestive Heart Failure *[see Warnings and Precautions (5.3)]*
- Hypertension *[see Warnings and Precautions (5.4)]*
- Pancreatitis *[see Dosage and Administration (2.3) and Warnings and Precautions (5.5)]*
- Hemorrhage *[see Warnings and Precautions (5.6)]*
- Fluid Retention *[see Warnings and Precautions (5.7)]*
- Cardiac Arrhythmias *[see Warnings and Precautions (5.8)]*
- Myelosuppression *[see Dosage and Administration (2.2) and Warnings and Precautions (5.9)]*

The adverse reactions described in this section were identified in a single-arm, open-label, international, multicenter trial in 449 patients with CML or Ph+ ALL whose disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy including those with the BCR-ABL T315I mutation. All patients received a starting dose of 45 mg Iclusig once daily. At the time of analysis, the median duration of treatment with Iclusig was 337 days in patients with CP-CML, 362 days in patients with AP-CML, 89 days in patients with BP-CML, and 81 days in patients with Ph+ ALL. The median dose intensity was 37 mg, or 83%, of the expected 45 mg dose.

Adverse reactions reported in more than 10% of all patients treated with Iclusig in this trial are presented in Table 4. Overall, the most common non-hematologic adverse reactions (≥ 20%) were hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, and pyrexia.

The rates of treatment-emergent adverse events resulting in discontinuation were 13% in CP-CML, 11% in AP-CML, 15% in BP-CML, and 9% in Ph+ ALL. The most common adverse events that led to treatment discontinuation were thrombocytopenia (4%) and infections (1%).

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17% of patients, but was much lower in group C, which did not receive chemotherapy (4 serious adverse events in 4% of patients).

The results of the TRYPHAENA trial were presented at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium,[2] and updated safety results were recently published in the journal *Annals of Oncology*. This study was a phase II, multicenter, open-label study that enrolled 225 patients with operable, locally advanced, or inflammatory breast cancer. Patients were randomized in a 1:1:1 ratio to receive 6 neoadjuvant cycles every 3 weeks. The first group, Arm A, received a regimen of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) followed by docetaxel, with trastuzumab and pertuzumab given concurrently throughout the treatment. Arm B received FEC followed by docetaxel plus trastuzumab and pertuzumab. Arm C received docetaxel and carboplatin plus trastuzumab and pertuzumab. After patients were treated with neoadjuvant therapy, they underwent surgery and continued on trastu-

Dose modifications (dose delays or dose reduction) due to adverse reactions occurred in 74% of the patients. The most common adverse reactions (≥5%) that led to dose modifications include thrombocytopenia (30%), neutropenia (13%), lipase increased (12%), rash (11%), abdominal pain (11%), pancreatitis (6%), and ALT, AST, or GGT increased (6%).

Table 4: Adverse Reactions Occurring in >10% of Patients, Any Group

	CP-CML (N=270)		AP-CML (N=85)		BP-CML (N=62)		Ph+ ALL (N=32)	
System Organ Class	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**
Cardiac or Vascular disorders								
Hypertension (a)	68	39	71	36	65	26	53	31
Arterial ischemia (b)	13	7	12	6	8	5	3	0
Cardiac Failure (c)	6	4	6	2	15	11	6	6
Gastrointestinal disorders								
Abdominal pain (d)	49	10	40	8	34	6	44	6
Constipation	37	2	24	2	26	0	47	3
Nausea	23	1	27	0	32	2	22	0
Diarrhea	16	1	26	0	18	3	13	3
Vomiting	13	2	24	0	23	2	22	0
Oral mucositis (e)	10	1	15	1	23	0	9	3
GI hemorrhage (f)	2	<1	8	1	11	5	9	6
Blood and lymphatic system disorders								
Febrile neutropenia	1	<1	4	4	11	11	25	25
Infections and infestations								
Sepsis	1	1	5	5	8	8	22	22
Pneumonia	3	2	11	9	13	11	9	3
Urinary tract infection	7	1	12	1	0	0	9	0
Upper respiratory tract infection	11	1	8	0	11	2	0	0
Nasopharyngitis	9	0	12	0	3	0	3	0
Cellulitis	2	1	4	2	11	3	0	0
Nervous system disorders								
Headache	39	3	28	0	31	3	25	0
Peripheral neuropathy (g)	13	2	8	0	8	0	6	0
Dizziness	11	0	5	0	5	0	3	0
Respiratory, thoracic, and mediastinal disorders								
Pleural effusion	3	1	11	2	13	0	19	3
Cough	12	0	17	0	18	0	6	0
Dyspnea	11	2	15	2	21	7	6	0
Skin and subcutaneous tissue disorders								
Rash and related conditions	54	5	48	8	39	5	34	6
Dry skin	39	2	27	1	24	2	25	0
Musculoskeletal and connective tissue disorders								
Arthralgia	26	2	31	1	19	0	13	0
Myalgia	22	1	20	0	16	0	6	0
Pain in extremity	17	2	17	0	13	0	9	0
Back pain	15	1	11	2	16	2	13	0
Muscle spasms	12	0	5	0	5	0	13	0
Bone pain	12	<1	12	1	11	3	9	3
General disorders and administration site conditions								
Fatigue or asthenia	39	3	36	6	35	5	31	3
Pyrexia	23	1	31	5	32	3	25	0
Edema, peripheral	13	<1	19	0	13	0	22	0
Pain	8	<1	7	0	16	3	6	3
Chills	7	0	11	0	13	2	9	0
Metabolism and nutrition disorders								
Decreased appetite	8	<1	12	1	8	0	31	0
Investigations								
Weight decreased	6	<1	7	0	5	0	13	0
Psychiatric disorders								
Insomnia	7	0	12	0	8	0	9	0

Adverse drug reactions, reported using MedDRA and graded using NCI-CTC-AE v 4.0 (NCI Common Terminology Criteria for Adverse Events) for assessment of toxicity.

Treatment-emergent, all causality events

(a) derived from blood pressure (BP) measurement recorded monthly while on trial

(b) includes cardiac, central nervous system, and peripheral arterial ischemia

(c) includes cardiac failure, cardiac failure congestive, cardiogenic shock, cardiopulmonary failure, ejection fraction decreased, pulmonary edema, right ventricular failure

(d) includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort

(e) includes aphthous stomatitis, lip blister, mouth ulceration, oral mucosal eruption, oral pain, oropharyngeal pain, pharyngeal ulceration, stomatitis, tongue ulceration

(f) includes gastric hemorrhage, gastric ulcer hemorrhage, hemorrhagic gastritis, gastrointestinal hemorrhage, hematemesis, hematochezia, hemorrhoidal hemorrhage, intra-abdominal hemorrhage, melena, rectal hemorrhage, and upper gastrointestinal hemorrhage

(g) includes burning sensation, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral sensorimotor neuropathy, polyneuropathy

Table 5: Serious Adverse Reactions (SAR)

	N (%)
Cardiovascular disorders	
Arterial ischemic event	34 (8%)
Myocardial infarction or worsening coronary artery disease	21 (5%)
Stroke or TIA	8 (2%)
Peripheral arterial disease	7 (2%)
Hemorrhage	22 (4%)
CNS hemorrhage	10 (2%)
Gastrointestinal hemorrhage	10 (2%)
Cardiac failure	20 (4%)
Effusions*	13 (3%)
Atrial fibrillation	11 (2%)
Venous thromboembolism	10 (2%)
Hypertension	8 (2%)
Gastrointestinal disorders	
Pancreatitis	23 (5%)
Abdominal pain	17 (4%)
Blood and lymphatic system disorders	
Febrile neutropenia	13 (3%)
Thrombocytopenia	13 (3%)
Anemia	12 (2%)
Infections	
Pneumonia	24 (4%)
Sepsis	11 (2%)
General	
Pyrexia	14 (3%)

*includes pericardial effusion, pleural effusion, and ascites

Laboratory Abnormalities

Myelosuppression was commonly reported in all patient populations. The frequency of grade 3 or 4 thrombocytopenia, neutropenia, and anemia was higher in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML (see Table 6).

Table 6: Incidence of Clinically Relevant Grade 3/4* Hematologic Abnormalities

Laboratory Test	CP-CML (N=270) (%)	AP-CML (N=85) (%)	BP-CML (N=62) (%)	Ph+ ALL (N=32) (%)
Hematology				
Thrombocytopenia (platelet count decreased)	36	47	57	47
Neutropenia (ANC decreased)	24	51	55	63
Leukopenia (WBC decreased)	14	35	53	63
Anemia (Hgb decreased)	9	26	55	34
Lymphopenia	10	26	37	22

ANC=absolute neutrophil count, Hgb=hemoglobin, WBC=white blood cell count

*Reported using NCI-CTC-AE v 4.0

Table 7: Incidence of Clinically Relevant Non-Hematologic Laboratory Abnormalities

Laboratory Test	Safety Population N=449	
	Any Grade* (%)	Grade 3/4 (%)
Liver function tests		
ALT increased	53	8
AST increased	41	4
Alkaline phosphatase increased	37	2
Albumin decreased	28	1
Bilirubin increased	19	1
Pancreatic enzymes		
Lipase increased	41	15
Amylase increased	3	<1
Chemistry		
Glucose increased	58	6
Phosphorus decreased	57	8
Calcium decreased	52	1
Sodium decreased	29	5
Glucose decreased	24	0
Potassium decreased	16	2
Potassium increased	15	2
Sodium increased	10	<1
Bicarbonate decreased	11	<1
Creatinine increased	7	<1
Calcium increased	5	0
Triglycerides increased	3	<1

ALT=alanine aminotransferase, AST=aspartate aminotransferase.

*Graded using NCI-CTC-AE v 4.0

7 DRUG INTERACTIONS

Based on *in vitro* studies ponatinib is a substrate of CYP3A4/5 and to a lesser extent CYP2C8 and CYP2D6. Ponatinib also inhibits the P-glycoprotein (P-gp), ATP-binding cassette G2 (ABCG2) [also known as BCRP], and bile salt export pump (BSEP) transporter systems *in vitro [see Clinical Pharmacology (12.3)]*.

zumab until they completed 1 year of treatment. The study was not powered to compare the 3 study arms.

The study found that the pCR rates were 61.6% in the concurrent group (A), 57.3% in the sequential group (B), and 66.2% in the anthracycline-free arm (C). The most common severe adverse events (AEs) observed in the 3 arms were neutropenia (47.2%, 42.7%, and 46.1%, in the 3 arms, respectively), leukopenia (19.4%, 12.0%, and 11.8%), and febrile neutropenia (18.1%, 9.3%, and 17.1%). Additional high AE rates observed with the anthracycline-free arm included anemia (17.1%), thrombocytopenia (11.8%), and diarrhea (11.8%). While these studies served as the primary basis for the September 12 ODAC vote, a combination of other studies, including the results of the CLEOPATRA trial in the metastatic setting as well as evidence supporting the use of pCR as an end point, served as the basis for the overwhelmingly positive vote.

"We need to look at the totality of the evidence…and not just one study," said Gary Lyman, MD, MPH, professor of Medicine and director of comparative effectiveness and outcomes research at Duke University School of Medicine and the Duke Comprehensive Cancer Center, and a temporary voting member of ODAC.

The ODAC members stressed to Genentech, the drug's manufacturer, that they are very interested in the results of the APHINITY trial. If the pertuzumab regimen is approved by the FDA but the results of the APHINITY trial are negative, ODAC recommended that the company voluntarily withdraw pertuzumab from the market for use in this neoadjuvant setting.

With many members of the public commenting on the life-changing experiences they had with pertuzumab, and others commenting on the need for earlier treatment options, the company is viewing the September 12 decision as a positive step in the future of this drug.

"More than 6000 people in the United States die of HER2-positive breast cancer each year," said Hal Barron, MD, chief medical officer and head, Global Product Development. "The ODAC's recommendation is a step toward bringing Perjeta to people with HER2-positive, early-stage breast cancer, where treatment can potentially prevent the disease from returning and spreading."

References

1. Gianni L, Pienkowski T, Im Y-H, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomized, multicenter, open-label, phase 2 trial. *Lancet Oncol.* 2012;13(1):25-32.

2. Schneeweiss A, Chia S, Hickish T, et al. Neoadjuvant pertuzumab and trastuzumab concurrent or sequential with an anthracycline-containing or concurrent with an anthracycline-free standard regimen: a randomized phase II study (TRYPHAENA). 2011 CTRC-AACR San Antonio Breast Cancer Symposium; December 6-10, 2011; San Antonio, Texas. Abstract S5-6.

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Melanoma Combination Granted Priority Review Designation by FDA

Christina Izzo

Last month, the US Food and Drug Administration (FDA) granted Priority Review to dabrafenib (Tafinlar) and trametinib (Mekinist) as a combination treatment for patients with unresectable or metastatic melanoma with a *BRAF*$^{V600E/K}$ mutation.

According to a September 16 statement from the drugs' manufacturer, GlaxoSmithKline, the FDA has set target dates in early January 2014 to review the trametinib and dabrafenib supplements. The drugs were approved simultaneously as single agents earlier this year.

Each drug treats melanoma through a different mechanism of action. Dabrafenib is a BRAF inhibitor approved to treat patients who express the *BRAF*^{V600E} mutation, while trametinib, a MEK 1/2 inhibitor, is approved to treat patients with either the *BRAFV*^{600E} or *BRAF*^{V600K} mutation. Both drugs act on the RAS kinase pathway, dabrafenib at an earlier point than trametinib. A patient will typically develop resistance to dabrafenib monotherapy after about 5 to 7 months. The addition of trametinib helps overcome the tumor's resistance mechanism, allowing for a more durable response to treatment

The Priority Review was granted based on the results of a randomized phase I/II study that compared combination therapy with dabrafenib and trametinib with dabrafenib monotherapy in adult patients with *BRAF*$^{V600E/K}$ mutation-positive metastatic melanoma.

According to the study that was published in the *New England Journal of Medicine*, progression-free survival (PFS), response rate, and duration of response favored the combination of dabrafenib and trametinib compared with single agent dabrafenib for patients with *BRAF*$^{V600E/K}$–positive metastatic melanoma.[1]

The phase II study randomized 162 patients with BRAFV600E/K–positive metastatic melanoma to 1 of 3 treatment arms: monotherapy with dabrafenib at 150 mg/BID; combination of dabrafenib at 150 mg/BID plus 1 mg of once-daily trametinib; or concurrent full doses of both drugs (dabrafenib at 150 mg/BID; once-daily trametinib at 2 mg). The median PFS for patients who received the full-dose combination was 9.4 months, as compared with 5.8 months with dabrafenib monotherapy (hazard ratio for progression or death, 0.39; 95% confidence interval, 0.25 to 0.62; P <.001).

Side effects associated with MEK inhibitors, including peripheral edema, hypertension, decreased cardiac ejection fraction, and ocular events, had a higher occurrence in the combination therapy, while side effects associated with BRAF inhibitors of hyperproliferative skin lesions occurred less frequently in the combination group compared with the monotherapy group.

In February 2013, the global phase III COMBI-AD study began, aiming to analyze the combination of dabrafenib and trametinib as adjuvant therapy for patients with melanoma.

The study will evaluate whether the combination of agents can delay or prevent the recurrence of melanoma (Relapse Free Survival) in patients with Stage IIIa, IIIb, or IIIc *BRAF*$^{V600E/K}$ mutation-positive melanoma that has been completely removed by surgery. The study will also evaluate the safety profile of the dabrafenib-trametinib combination in this treatment setting.

"The patients included in this trial are at high risk of their melanoma returning after surgery and there are currently few treatment options to reduce this risk," Rafael Amado, MD, head of Oncology Research and Development for GlaxoSmithKline, said in a statement when the trial was announced. "Given the efficacy and safety findings observed with combined dabrafenib-trametinib treatment in the metastatic setting, we are investigating whether the combination administered after surgery can help these patients live longer without melanoma recurrence."

There are 2 additional phase III studies ongoing, aimed to evaluate the combination of dabrafenib and trametinib for patients with metastatic BRAFV600 melanoma.

Reference

1. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med.* 2012; 367:1694-1703. doi:10.1056/NEJMoa1210093

Volasertib Given Breakthrough Therapy Designation

Silas Inman

The novel polo-like kinase 1 (PLK1) inhibitor volasertib in combination with low-dose cytarabine (LDAC) received a breakthrough therapy designation September 17 from the US Food and Drug Administration (FDA) for its potential as a treatment for patients with untreated acute myeloid leukemia (AML) who are ineligible for intensive remission induction therapy.

PLKs function as important regulators of the cell cycle and are involved in the activation of cyclin-dependent kinases and maintenance of genomic stability. In preclinical evidence exploring the PLK family, PLK1 was identified as holding the most potential for targeted cancer therapies, since it is commonly overexpressed in many tumor types. As an antimitotic target, PLK1, which is only expressed in dividing cells, plays an essential role throughout many stages of mitosis. As an antagonist of PLK1, the first-in-class agent volasertib is thought to induce mitotic arrest and apoptosis in cancer cells.

The FDA's breakthrough therapy designation will help expedite Boehringer Ingelheim's development of volasertib. The program is intended to potentially speed up the review process for treatments for serious or life-threatening conditions. This relatively new designation provides similar benefits to the FDA's fast-track designation, although the 2 are separate programs. Unlike the fast-track designation, a breakthrough therapy must demonstrate preliminary clinical evidence and represent a substantial improvement over available therapies.

Unlike the fast-track designation, a breakthrough therapy must demonstrate preliminary clinical evidence and represent a substantial improvement over available therapies.

"This FDA breakthrough therapy designation provides Boehringer Ingelheim the opportunity to engage in an ongoing dialogue with the FDA to help expedite the development of volasertib as a potential treatment option for these patients with AML," said Sabine Luik, MD, the senior vice president of Medicine & Regulatory Affairs and the US regional medical director for Boehringer Ingelheim Pharmaceuticals, Inc, in a statement issued by the company.

The breakthrough therapy designation was granted based on results from a phase II study presented at the 2012

American Society of Hematology annual meeting. In this study, patients with previously untreated AML who were ineligible for intensive treatment were randomized to receive either intravenous volasertib in combination with LDAC or LDAC alone. Preliminary results from the trial demonstrated significant improvement in the primary end point of objective response (measured as complete remission (CR) or CR with incomplete blood count recovery (CRi). Additionally, a trend was observed in favor of the combination for the secondary end point of event-free survival (EFS).[1]

In the study, 87 patients were randomized in a 1:1 ratio to receive volasertib plus LDAC (n = 42) or LDAC alone (n = 45). Treatment was repeated every 4 weeks until progression for a median of 2 cycles. The maximum tolerated dose for volasertib of 350 mg was administered on days 1 and 15 and LDAC was administered at 20 mg twice daily subcutaneously on days 1 to 10. The median age for patients in the trial was between 75 and 76 years.

At the time of the analysis, 31% of patients receiving the combination achieved a CR or CRi compared with 11.1% in the control arm (odds ratio 3.59; 95% CI, 1.15-11.18]; *P* = .0277). The median time to remission in the volasertib arm was 71 days compared with 69 days in the control arm.

A trend toward an advantage in EFS was observed in the volasertib arm, with a median EFS of 169 days compared with 69 days for patients who received LDAC alone (hazard ratio [HR] = .61; 95% CI, 0.35 - 1.05; *P* = .0725). At the time of the analysis, the secondary end point of overall survival was not yet available, since only 2 patients had experienced recurrence or death. In total, the remission duration with the combination was 53 to 407 days compared with 32 to 282 days with LDAC alone.

Adverse events were more frequent with the combination of volasertib and LDAC and were in line with those expected with the agent's myelosuppressive mechanism of action. However, early death rates were similar between the 2 arms at 30, 60, and 90 days.

The most common all-grade events observed in patients who received volasertib combination were febrile neutropenia (50%), constipation (45.2%), nausea (40.5%), and anemia (40.5%). The most common events observed in the LDAC arm were nausea (33.3%), anemia (28.9%), pyrexia (28.9%), constipation (26.7%), asthenia (26.7%), and diarrhea (26.7%) in the LDAC arm. In all, 95.2% of patients experienced grade 3 or higher events with the combination compared with 68.9% with LDAC alone.

Following the presentation of these findings, a phase III confirmatory analysis was initiated in January 2013. In this study, labeled POLO-AML-2, volasertib plus LDAC is being compared with LDAC and placebo as a treatment specifically for patients 65 years or older with previously untreated AML who are ineligible for intensive remission induction therapy. The trial is currently enrolling patients with the first patient entering the trial in February 2013.

In addition to volasertib, Boehringer Ingelheim is investigating several agents in phase III clinical trials for a variety of diseases, including non-small cell lung cancer (NSCLC), breast cancer, ovarian cancer, and head and neck cancer. In July 2013, the company received its first oncology approval for afatinib as a treatment for patients with *EGFR*-mutant advanced NSCLC.

"Volasertib is one of many investigational compounds in Boehringer Ingelheim's growing oncology pipeline and is an example of our commitment to exploring treatment approaches with the goal of improving patient outcomes," Luik said in a release.

Reference

1. Maertens J, Lübbert M, Fiedler W, et al. Phase I/II study of volasertib (BI 6727), an intravenous polo-like kinase (PLK) inhibitor, in patients with acute myeloid leukemia (AML): results from the randomized phase II part for volasertib in combination with low-dose cytarabine (LDAC) versus LDAC monotherapy in patients with previously untreated AML ineligible for intensive treatment. Presented at: 54th American Society of Hematology Annual Meeting and Exposition; Dec 8-11, 2012; Atlanta, Georgia. Abstract 411.

Ofatumumab Receives Breakthrough Therapy Designation for Earlier Use in CLL

Ben Leach

The monoclonal antibody ofatumumab (Arzerra) has received breakthrough therapy designation from the US Food and Drug Administration (FDA) that could allow for earlier use in patients with chronic lymphocytic leukemia (CLL), according to a joint announcement released by GlaxoSmithKline and Genmab, who have a co-development and commercialization agreement for distributing the drug.

In 2009, ofatumumab was approved for the treatment of CLL that can no longer be controlled by other forms of chemotherapy. This breakthrough therapy designation is for patients who have not received prior treatment and are inappropriate for fludarabine-based therapy.

The breakthrough therapy designation comes on the heels of positive phase III data for ofatumumab that were announced in May. In this study, 447 with previously untreated CLL were randomized to receive either ofatumumab in combination with chlorambucil or chlorambucil alone. The study found that patients in the ofatumumab experienced a median progression-free survival of 22.4 months compared with 13.1 months in the control arm (hazard ratio [HR] = 0.57; *P* <.001). The study met its primary endpoint, and there were no unexpected safety findings. Full results for the study have been submitted for presentation at the 2013 American Society of Hematology (ASH) Annual Meeting and Exposition, taking place in December in New Orleans, Louisiana.

Ofatumumab is a human monoclonal antibody that targets the CD20 protein, which is expressed on the surface of both normal and malignant B-cells. This mechanism of action allows for a greater response from the immune system against these cancerous cells.

"We are exceedingly proud to receive the breakthrough therapy designation, the second this year for GSK," said Kathy Rouan, PhD, vice president and head of biopharmaceutical development at GlaxoSmithKline, in a statement. "This FDA program is intended to expedite not just the development but also the review of drugs for serious or life-threatening conditions. We are actively working on our submission and look forward to the enhanced regulatory interaction allowed for breakthrough therapies."

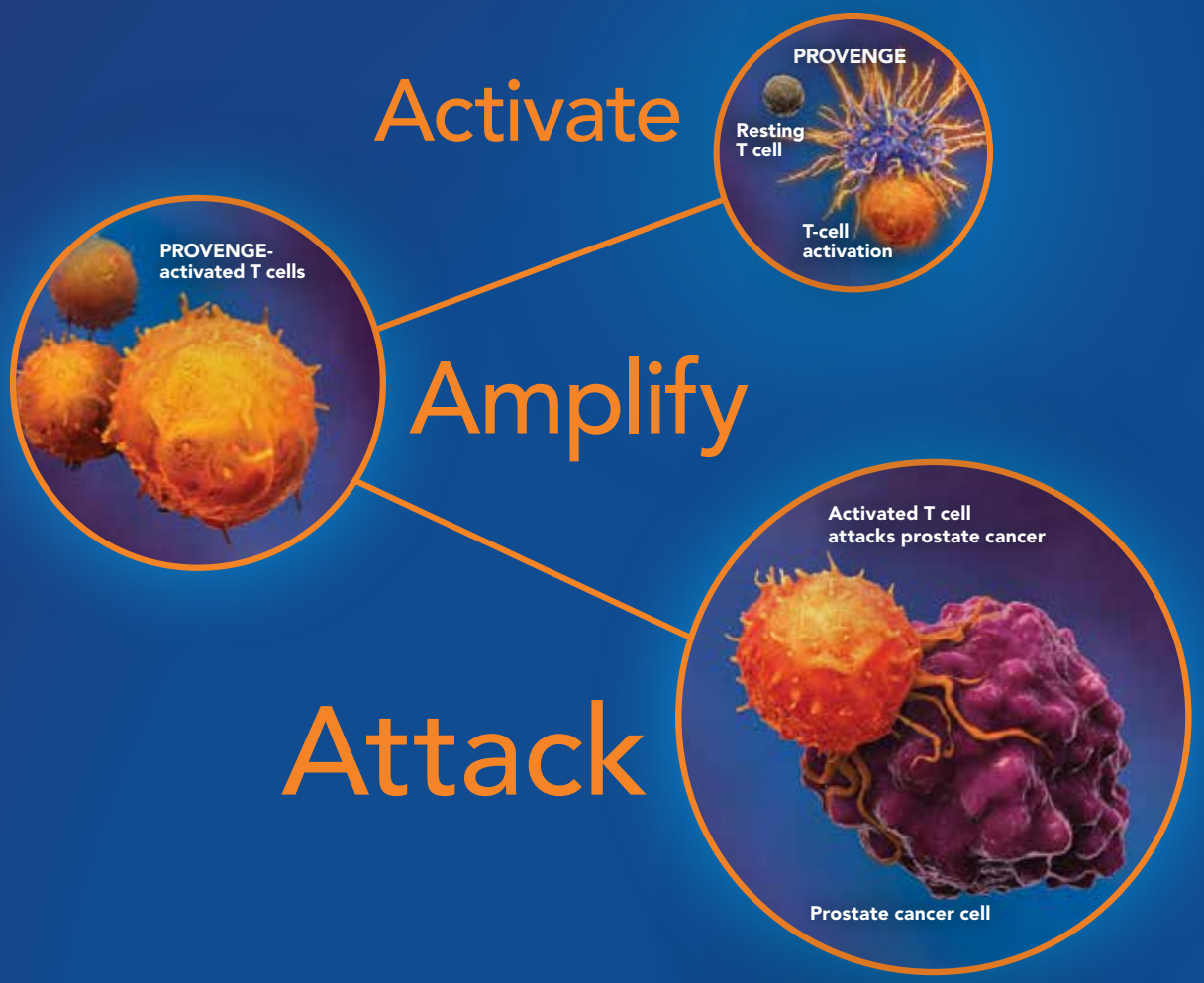
Jan van de Winkel, PhD

Breakthrough therapy designation can be assigned to drugs that appear to be superior to existing treatments for life-threatening conditions. Drugs that receive this designation are allowed an expedited review process, aided by more meetings between the FDA and the manufacturer during the development process, as well as requiring fewer patients for clinical trials and less time needed to conduct these trials. Ofatumumab is still eligible for fast-track designation, accelerated approval, and priority review, if GlaxoSmithKline and Genmab decide that they want to pursue any of these other designations.

"Both of Genmab's lead products, ofatumumab and daratumumab, have now been granted breakthrough therapy designations from the FDA," said Jan van de Winkel, PhD, chief executive officer of Genmab, in a statement. "This designation for ofatumumab reflects Genmab's mission to create differentiated products aimed at improving the lives of patients suffering from debilitating diseases and for whom existing treatments are inadequate."

In advanced prostate cancer

TREAT FIRST LINE WITH PROVENGE TO



EXTEND SURVIVAL

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

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

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

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

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

www.PROVENGE.com

PROVENGE®
(sipuleucel-T)

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

BRIEF SUMMARY – See full Prescribing Information for complete product information

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

DOSAGE AND ADMINISTRATION

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

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

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

(Table 1 continued on next page.)

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

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

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

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

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

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

Dendreon Corporation
Seattle, Washington 98101

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

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PROVENGE®
(sipuleucel-T)

THE AMERICAN JOURNAL OF MANAGED CARE®

First Generic Version of Capecitabine Gains FDA Approval

Silas Inman

The FDA has approved the first generic formulation of capecitabine (Xeloda), an oral chemotherapeutic that is currently approved to treat patients with metastatic colorectal cancer (mCRC) and metastatic breast cancer (MBC).

Genentech manufactures capecitabine, which became the first approved oral chemotherapy in 1998. The generic version of capecitabine will be marketed by Teva Pharmaceuticals USA at 150 and 500 mg doses. According to the FDA, on average, the cost of a generic drug is 80% to 85% lower than the brand name equivalent, amounting to billions of dollars saved on prescription drugs each year.

Kathleen Uhl, MD

The patent for capecitabine is set to expire on December 14, 2013. The global sales for the agent have continued to rise since its approval. It is considered a "blockbuster" drug, a distinction reserved for treatments that generate more than $1 billion in annual revenue. To date, a generic version of the drug has not been made available.

"Generic drugs are important options that allow greater access to healthcare for all Americans," said Kathleen Uhl, MD, the acting director of the Office of Generic Drugs in the FDA's Center for Drug Evaluation and Research. "This medication is widely used by people living with cancer, so it is important to have access to affordable treatment options.

"Since its initial approval in MBC, capecitabine has become widely utilized in several settings. The drug is most well known for its use in combination strategies, specifically in HER2-positive MBC, where it is commonly administered along with lapatinib (Tykerb). As a single-agent, capecitabine has demonstrated efficacy as a first-line therapy for patients with mCRC, following complete resection of the primary tumor when fluoropyrimidine therapy is preferred, and as a treatment for patients with HER2-negative MBC following prior treatment with anthracyclines and taxanes.

Even though the drug has been widely available for more than a decade, investigators are continuing to assess the drug's efficacy in multiple ongoing clinical trials. As of today's approval, the chemotherapy is being examined in combination or as a single-agent in over 300 open studies across a variety of diseases. Although the drug is not specifically FDA approved for other indications outside of breast cancer and colorectal cancer, capecitabine is widely used as a treatment for patients with gastric cancer in the first-line setting and in combination with oxaliplatin for patients with stage II to IIIb disease.

The standard schedule for capecitabine is 8 cycles of 1250 mg/m^2 administered orally twice daily for 2 weeks followed by 1 week of rest. The most common adverse reactions with capecitabine are diarrhea, hand-and-foot syndrome, nausea, and vomiting. Additionally, the medication has a boxed warning regarding an adverse capecitabine and anticoagulant interaction. **EBO**

Safety Concerns Halt Ponatinib Development

Silas Inman

The FDA has placed a partial hold on the clinical development of the BCR-ABL inhibitor ponatinib (Iclusig) as it investigates the high occurrence of arterial thrombosis in patients treated with the drug. As part of this hold, new patient enrollment into all clinical trials investigating ponatinib has been stopped.

Ponatinib was granted accelerated approval in December 2012 at a 45-mg daily dose for patients with chronic myeloid leukemia (CML) or Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ALL). This approval was based on data from the phase II PACE trial that enrolled patients who were resistant or intolerant to dasatinib or nilotinib, or harbored a *T315I* mutation.

A Boxed Warning was included in the approval, based on the development of arterial thrombosis in 8% of patients and hepatotoxicity in the trial. However, at an FDA-required median 24-month planned follow-up, the rate of arterial thrombosis had increased to 11.8% in patients treated with ponatinib, warranting the pause in patient enrollment.

Ariad Pharmaceuticals, Inc, the company developing ponatinib, is seeking the approval of dose modification from the FDA, in order to resume its ongoing clinical development program. Additionally, the company is consulting with the FDA on needed adjustments to the drug's prescribing information to reflect the newly discovered increase in toxicity.

"We believe that the actions we are taking will help us ensure the most appropriate and safe use of Iclusig. With 2 years of follow-up, we have learned a great deal about both the efficacy and safety of Iclusig in patients with Philadelphia-positive leukemias," stated Harvey J. Berger, MD, chairman and chief executive officer of Ariad.

The PACE trial was a single-arm investigation of 449 patients, of which 444 were eligible for efficacy analysis. The primary end point for patients with chronic-phase (CP)-CML (n = 267) was major cytogenetic response (MCyR). The primary end point was major hematologic response (MaHR) for patients with accelerated-phase (AP)-CML (n = 83), blast-phase (BP)-CML (n = 62), and Ph+ALL (n = 32).

Ponatinib was approved based on a 10-month analysis of the PACE trial that found that treatment with ponatinib demonstrated a 54% MCyR rate in patients with CP-CML. Specifically, 70% of the 64 patients with the *BCR-ABL T315I* mutation achieved MCyR. The MaHR rate was 52% in patients with AP-CML, 31% in patients with BP-CML, and 41% in patients with Ph+ ALL.

At this early follow-up, the median duration of MCyR for patients with CP-CML had not yet been reached. The median duration of MaHR was 9.5 months in patients with AP-CML, 4.7 months in patients with BP-CML, and 3.2 months in patients with Ph+ ALL.

At the 24-month follow-up, the PACE trial data demonstrated continued efficacy, even following dose reductions. Overall, 190 patients with CP-CML received a reduced dose of either 30 mg or 15 mg. Despite this reduction, 90% of patients who achieved MCyR maintained this response for a median of 19 months. Furthermore, Ariad noted in a release, for the 35 patients reduced to a 15-mg dose, 94% maintained a MCyR.

The most common adverse events were thrombocytopenia, rash, and dry skin. The most common serious adverse event was pancreatitis, which led to 1 patient discontinuing the drug. At 24 months, serious venous occlusion occurred in 2.9% of ponatinib-treated patients, compared with 2.2% when the drug was approved. In total, all types of arterial and venous-related adverse events occurred in approximately 20% of ponatinib-treated patients.

"We are focused first and foremost on the needs of cancer patients—to have new medicines that provide both safe and effective treatment of their malignancies. Our unwavering commitment to patients has led us to promptly take the steps we have outlined."

Harvey J. Berger, MD

"We are focused first and foremost on the needs of cancer patients—to have new medicines that provide both safe and effective treatment of their malignancies. Our unwavering commitment to patients has led us to promptly take the steps we have outlined," Berger said in a statement.

To support the accelerated approval of ponatinib, the phase III EPIC trial was initiated to compare 45 mg ponatinib with imatinib for patients with newly diagnosed CML. As a result of the new safety findings, Ariad, in collaboration with a data monitoring committee, is proposing that the daily dose of ponatinib be adjusted to 30 mg daily in this trial. However, if patients have already achieved a major molecular response (MMR), the dose will be further reduced to 15 mg daily. Additionally, the company announced, the eligibility criteria for all ponatinib clinical trials will be modified to exclude patients with prior arterial thrombosis that has resulted in heart attack or stroke. **EBO**

Positive Idelalisib Data End Late-Stage CLL Trial

Silas Inman

A phase III study of the PI3K-delta inhibitor idelalisib in combination with rituximab (Rituxan) has been stopped early following a positive interim analysis, according to a statement from Gilead Sciences, Inc, the company developing the drug announced October 10.

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

Idelalisib is a first-in-class selective

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

Indication and Important Safety Information for VELCADE® (bortezomib)

INDICATION

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

CONTRAINDICATIONS

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

WARNINGS, PRECAUTIONS, AND DRUG INTERACTIONS

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

In treating multiple myeloma

What is the value of VELCADE® (bortezomib)?

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

IF YOU DEFINE VALUE AS AN OVERALL SURVIVAL ADVANTAGE:

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

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

IF YOU DEFINE VALUE AS DEFINED LENGTH OF THERAPY:

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

IF YOU DEFINE VALUE AS MEDICATION COST:

- Medication cost is an important factor when considering overall drug spend. The Wholesale Acquisition Cost for VELCADE is $1,544 per 3.5-mg vial as of July 2013
- When determining the value of a prescription drug regimen, it may be worth considering medication cost, length of therapy, and dosing regimens. This list is not all-inclusive; there are additional factors to consider when determining value for a given regimen

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

ADVERSE REACTIONS

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

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

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

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

*Melphalan+prednisone.

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

VELCADE®
(bortezomib) FOR INJECTION

VELCADE®
(bortezomib) FOR INJECTION

Brief Summary

INDICATIONS:

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

CONTRAINDICATIONS:

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

WARNINGS AND PRECAUTIONS:

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

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

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

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

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

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

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

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

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

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

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

ADVERSE EVENT DATA:

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

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

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

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

DRUG INTERACTIONS:

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

USE IN SPECIFIC POPULATIONS:

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

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

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

Patients with Renal Impairment: The pharmacokinet VELCADE are not influenced by the degree of renal impai Therefore, dosing adjustments of VELCADE are not nec for patients with renal insufficiency. Since dialysis may r VELCADE concentrations, VELCADE should be administere the dialysis procedure. For information concerning dos melphalan in patients with renal impairment, see manufac prescribing information.

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

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

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

Takeda MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

V-12-0306a

(continued from SP317)

PI3K-delta inhibitor. This mechanism of action is thought to be effective in B-cell malignancies due to the role of PI3K-delta in the activation, proliferation, and survival of B cells. Prior to the phase III investigation, the treatment was explored in early-stage trials, which seemed to confirm this rationale.

Norbert W. Bischofberger, PhD

"This is the first phase III study to report positive results for a new class of targeted therapies that inhibit B-cell receptor signaling as a major component of their mechanism of action, an important area of focus in the development of chemotherapy-free regimens in CLL and other B-cell malignancies."

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

The phase III study enrolled a total of 220 patients, approximately 20 patients more than expected. All patients enrolled on the trial had previously treated recurrent CLL with measurable lymphadenopathy. Patients in the trial were randomized in a 1:1 ratio to receive idelalisib at a 150-mg dose twice daily in combination with intravenous rituximab at an initial dose of 375 mg/m^2 followed by 500 mg/m^2 or rituximab and placebo. Patients who progressed were eligible to receive idelalisib therapy in a double-blind extension study. Data from the interim analysis are likely to be presented later this year.

"Given the significant unmet medical need in CLL, particularly in this population of patients who are not fit for chemotherapy, we are pleased that idelalisib has shown a clinically meaningful benefit for patients," said Bischofberger in a statement.

The phase III study was launched on the basis of results from a phase I trial examining the combination of idelalisib with rituximab and/or bendamustine for patients with previously treated CLL. Results from this analysis were presented at the 2012 meeting of the American Society of Hematology.

In that study, 19 patients who had received a median of 2 prior therapies took idelalisib at 150 mg twice daily in combination with weekly rituximab at 375 mg/m^2. In the intent-to-treat to population, the overall response rate (ORR) was 78%. Moreover, the 1-year PFS rate was 74%, and 84% of patients experienced a lymph node response (shrinkage ≥50%) resulting in marked reductions in lymphadenopathy.

The highest level of response in this trial was experienced with the combination of idelalisib, rituximab, and bendamustine (Treanda). This portion of the trial contained 15 patients and found an ORR of 87%, a 1-year PFS rate of 87%, and lymph node response in 87% of patients. A randomized phase III study examining the combination of idelalisib, rituximab, and bendamustine is recruiting patients with previously treated CLL (NCT01569295).

"The high overall response rate and durable disease control observed in this phase II study suggest that idelalisib in combination with rituximab could become an important therapeutic option for CLL patients new to treatment."

The early stop of the phase III trial indicates a promising treatment with the potential for regulatory approval. However, controversy exists in medical research regarding stopping randomized clinical trials early based on evidence of benefit. In many cases, evidence suggests that trials that stop early overestimate treatment effects. Moreover, an analysis published in *BMJ* in 2012 found that large overestimates of benefits were common when less than 200 events were analyzed.

Most recently, a large phase III trial analyzing abiraterone acetate for men with metastatic castration-resistant prostate cancer before chemotherapy fell under scrutiny after the trial was halted early following an interim analysis. As a result of this early unblinding, many questioned the authenticity of the survival advantage experienced in the trial, since statistical significance had not been met. Despite this, the US Food and Drug Administration (FDA) approved abiraterone based on results from this study.

In its announcement, Gilead stated that it has informed the FDA of its decision to stop the trial. The company is engaged in conversations regarding a potential regulatory filing for idelalisib in CLL. In September 2013, Gilead submitted a New Drug Application to the FDA for approval of idelalisib for the treatment of patients with indolent non-Hodgkin's lymphoma (iNHL).

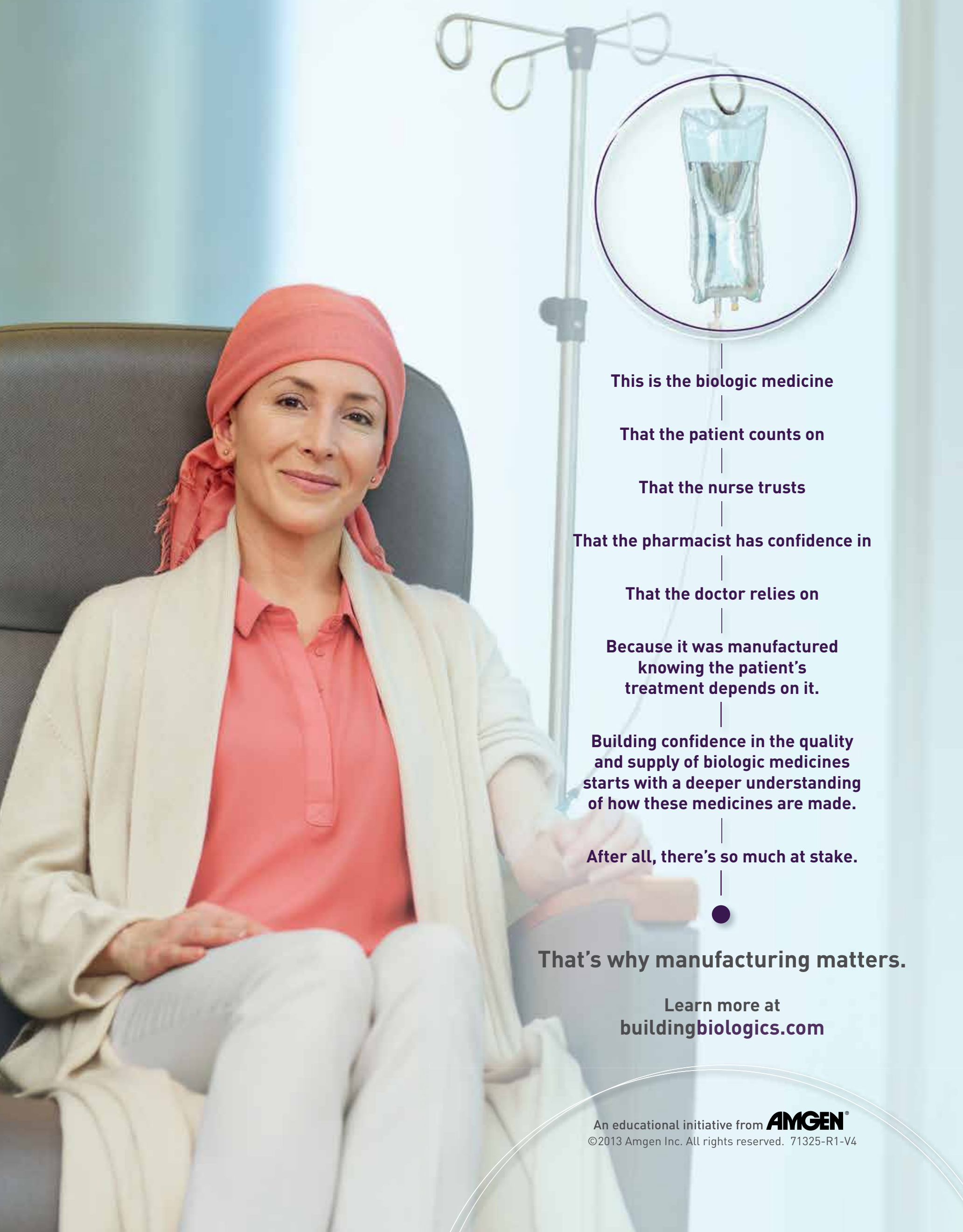
That submission was based on data from a single-arm, open-label phase II study of 125 patients with iNHL who were refractory to rituximab and alkylating-agent-containing chemotherapy. In an interim analysis of this study, single-agent idelalisib achieved an ORR of 53.6%, with a median duration of response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

In addition to previously treated patients with CLL and iNHL, idelalisib plus rituximab has demonstrated promising results in treatment-naïve patients with CLL, according to results from a phase II trial that was presented at the 2013 ASCO Annual Meeting.

In that study, patients who were ≥65 years old with previously untreated CLL or small lymphocytic lymphoma received idelalisib at 150 mg BID combined with weekly rituximab at 375 mg/m^2. At a 24-month analysis, the combination was found to be highly active in treatment-naïve elderly patients. The trial found a Kaplan-Meier estimated PFS benefit of 93%. Moreover, the combination achieved a complete response rate of 19% and an ORR of 97%.

Susan M. O'Brien, MD

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



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